1	FOOD AND DRUG ADMINISTRATION
2	CENTER FOR TOBACCO PRODUCTS
3	
4	
5	TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE
6	(TPSAC)
7	
8	
9	Friday, July 22, 2011
10	8:00 a.m. to 11:30 a.m.
11	
12	
13	
14	9200 Corporate Boulevard
15	Rockville, Maryland
16	
17	
18	
19	
20	This transcript has not been edited or corrected, but
21	appears as received from the commercial transcribing
22	service.

1	Meeting Roster	
2	Dissolvable Tobacco Products Session	
3	TPSAC Members (voting, Special Government Employee)	
4	Jonathan M. Samet, M.D., M.S. (Chair)	
5	Professor and Flora L. Thornton Chair	
6	Department of Preventive Medicine	
7	Keck School of Medicine	
8	University of Southern California, Los Angeles	
9	Norris Comprehensive Cancer Center	
10	1441 Eastlake Avenue, Room 4436, MS 44	
11	Los Angeles, California 90089	
12		
13	Neal L. Benowitz, M.D.	
14	Professor	
15	Chief, Division of Clinical Pharmacology	
16	Departments of Medicine and Biopharmaceutical	
17	Sciences	
18	Schools of Medicine and Pharmacy	
19	University of California, San Francisco, Box 1220	
20	San Francisco, California 94143-1220	
21		
22		

1	Mark Stuart Clanton, M.D., M.P.H.
2	(participating by telecom)
3	Chief Medical Officer
4	American Cancer Society, High Plains Division
5	2433-A Ridgepoint Drive
6	Austin, Texas 78754
7	
8	Karen L. DeLeeuw, M.S.W.
9	(Employee of a state or local government or of the
10	Federal Government)
11	Director, Center for Healthy Living and Chronic
12	Disease Prevention
13	Colorado Department of Public Health and
14	Environment
15	4300 Cherry Creek Drive South
16	Denver, Colorado 80246
17	
18	
19	
20	
21	
22	

```
1
      Patricia Nez Henderson, M.P.H., M.D.
      (Representative of the general public)
2
     Vice President
3
     Black Hills Center for American Indian Health
4
      701 St. Joseph Street, Suite 204
5
     Rapid City, South Dakota 57701
6
7
      TPSAC Members (non-voting Industry Representatives)
8
9
     Luby Arnold Hamm, Jr.
      (Representative of the interests of tobacco
10
11
     growers)
      4901 Shallowbrook Trail
12
     Raleigh, North Carolina 27616-6107
13
14
15
      Jonathan Daniel Heck, Ph.D., DABT
16
      (Representative of the tobacco manufacturing
17
      industry)
18
     Lorillard Tobacco Company
19
     A.W. Spears Research Center
      420 N. English St., P.O. Box 21688
20
     Greensboro, North Carolina 27420-1688
21
22
```

1	John H. Lauterbach, Ph.D., DABT
2	(Representative for the interest of small business
3	tobacco manufacturing industry)
4	Lauterbach & Associates, LLC 211 Old Club Court
5	Macon, Georgia 31210-4708
6	
7	Ex Officio Members (non-voting)
8	Dana M. Shelton, M.P.H.
9	Associate Director for Policy
10	Centers for Disease Control and Prevention
11	4770 Buford Highway NE
12	Mailstop K-50
13	Atlanta, Georgia 30341
14	
15	Mirjana Djordejevic, Ph.D.
16	Program Director
17	Tobacco Control Research Branch
18	Behavioral Research Program
19	National Cancer Institute
20	National Institutes of Health
21	9000 Rockville Pike
22	Bethesda, Maryland 20892

1	Temporary Members (voting)
2	Robert Balster, Ph.D.
3	Director, Institute for Drug and Alcohol Studies
4	Virginia Commonwealth University
5	P.O. Box 980310
6	Richmond, Virginia 23298
7	
8	Fred Pampel, Ph.D.
9	Professor of Sociology and Research Associate
10	Institute of Behavioral Science, Population Program
11	484UCB
12	University of Colorado
13	Boulder, Colorado 80304
14	
15	Consultant (nonvoting)
16	Bruce Simons-Morton, Ed.D., M.P.H.
17	Branch Chief and Senior Investigator
18	Division of Epidemiology Statistics and
19	Prevention Research
20	National Institutes of Health
21	Bethesda, Maryland 20892
22	

1	FDA Participants at the table (non-voting)
2	
3	David L. Ashley, Ph.D.
4	Director, Office of Science
5	Center for Tobacco Products
6	Food and Drug Administration
7	9200 Corporate Boulevard
8	Rockville, Maryland 20850-3229
9	
10	
11	Sarah E. Evans, Ph.D.
12	Social Scientist
13	CTP/FDA
14	
15	
16	
17	
18	
19	
20	

1	CONTENTS	
2	AGENDA ITEM	PAGE
3	Call to Order	
4	Jonathan Samet, M.D., M.S.	9
5	Conflict of Interest Statement	
6	Caryn Cohen, M.S.	10
7	Introduction of Committee Members	14
8	FDA Presentation	
9	Dissolvable Tobacco Products	
10	Sarah Evans, Ph.D.	16
11	Committee Discussion	31
12	Open Public Hearing	51
13	Committee Discussion of Questions to the	
14	Committee and Next Steps	123
15	Adjournment	181
16		
17		
18		
19		
20		
21		
22		

PROCEEDINGS

(8:02 a.m.)

Call to Order

DR. SAMET: Good morning. I want to welcome everyone back to the second day of the TPSAC meeting. I think we're fortunate. I understand that this is the only place with working air conditioning in the building, or formerly working.

If it fails, we'll just all sit here like -
Well, we're back, and we're going until noon

today. I need to make a few statements.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members

take care that their conversations about the topics

at hand take place in the open forum of the

meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during the break.

Thanks.

Conflict of Interest Statement

MS. COHEN: The Food and Drug Administration is convening today's meeting of the Tobacco

Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and non-voting members are special government employees or regular federal employees from other agencies and are subject to

federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by, but not limited to, those found in 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC

Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential conflicts when necessary to afford

the committee essential expertise.

Related to the discussions of today's meeting, members of this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the nature and impact of the use of dissolvable tobacco products on public health. These discussions will begin the process for TPSAC's required report to the Secretary of Health and Human Services regarding the issue of the nature and impact of the use of dissolvable tobacco products on public health, including such use among children.

This is a particular matters meeting during which general issues will be discussed. Based on

the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all committee members to disclose any public statements that they may have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Daniel Heck and Dr. John Lauterbach and Mr. Arnold Hamm are participating in this meeting as non-voting industry representatives acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively.

Their role at this meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company, Dr. Lauterbach is employed by Lauterbach & Associates, LLC, and Mr. Hamm is retired.

FDA encourages all other participants to

advise the committee of any financial relationships 1 that you may have with any firms at issue. 2 I would like to remind everyone to please 3 4 turn off your cell phones during the meeting. if you're on the phone, please keep your phone on 5 mute unless you're speaking. 6 Now, I'd like to identify the FDA press 7 contacts. They are Stephanie Yao and Michelle 8 Bolek. 9 Please stand up. Thank you. 10 Introduction of Committee Members 11 DR. SAMET: Let me ask for a quick 12 introduction, a round of introductions from the 13 committee. 14 Dan, why don't we start with you? 15 16 DR. HECK: Dan Heck, Lorillard Tobacco, representing the manufacturers. 17 18 DR. LAUTERBACH: John Lauterbach, 19 Lauterbach & Associates, representing the small business tobacco product manufacturers. 20 MR. HAMM: Arnold Hamm, representing U.S. 21 22 tobacco growers.

DR. DJORDJEVIC: Mirjana Djordjevic, with 1 the National Cancer Institute, representing 2 National Institutes of Health. 3 4 MS. SHELTON: Good morning. Dana Shelton, with the Office on Smoking and Health at CDC, 5 representing the Centers for Disease Control. 6 DR. EVANS: Sarah Evans, Center for Tobacco 7 Products. 8 DR. ASHLEY: David Ashley, Center for 9 Tobacco Products. 10 DR. BALSTER: I'm Robert Balster from 11 Virginia Commonwealth University. Incidentally, I 12 see that my listing on the listing of members here 13 is Robert T. Balster, when, in fact, my dad, Louis, 14 15 after whom I'm named, Robert Louis Balster, would So it's Robert L. Balster. 16 be upset. DR. NEZ HENDERSON: Patricia Nez Henderson, 17 18 Black Hills Center for American Indian Health. DR. PAMPEL: Fred Pampel, the University of 19 Colorado at Boulder. 20 21 DR. SIMONS-MORTON: Bruce Simons-Morton, 22 National Institute of Child Health and Human

Development. 1 DR. BENOWITZ: Neal Benowitz, University of 2 California, San Francisco. 3 4 MS. DELEEUW: Karen DeLeeuw, Colorado Department of Public Health and Environment, 5 representing state government. 6 7 DR. SAMET: Let's see. Mark, are you on the phone? 8 DR. CLANTON: Mark Clanton, 9 I am. pediatrics, public health and oncology. 10 DR. SAMET: Good. 11 Thank you. Sarah? 12 FDA Presentation - Sarah Evans 13 DR. EVANS: Good morning, everyone. 14 It is 15 true that the air conditioning is out upstairs. 16 I'm happy to see many of my FDA colleagues in the audience this morning. 17 18 [Laughter.] My name is Sarah Evans. 19 DR. EVANS: Welcome to the second day of the third round of TPSAC. The 20 topic this time will be dissolvable tobacco 21 22 products, and I am the leading scientist on this

effort. And, as you know, the information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.

I'd like to begin today with an overview of FDA activities on dissolvable tobacco products.

Today I'll be talking about information available to FDA, FDA research activities, and other FDA activities.

Currently, information available to FDA includes published peer-reviewed literature, submissions to dockets, responses to FDA's February 1st, 2010 letter, and private meetings requested with industry.

FDA conducted a literature search. As of July 1st, 22 peer-reviewed articles regarding dissolvable tobacco products were found using six databases, including PubMed. These articles were included in your background materials, and the

search terms included "dissolvable tobacco, novel, strip, stick, pellet, Orbs," and brand names of products by manufacturers. Types of studies included in these articles were clinical studies, cross-sectional studies, focus groups, and biomarker studies.

FDA did request comments in a public document. We asked for information on impact of dissolvable tobacco use on public health. This information was also included in your background materials. These responses included survey data, industry comments, health association and state government comments, and individual comments.

On February 1st, 2010, FDA issued a letter to Star Scientific and R.J. Reynolds. To FDA's knowledge, only these two companies were marketing dissolvable products at that time. Both companies did respond to our letter.

In the letter, FDA asked for a comprehensive and detailed summary of research activities and findings on perceptions and comprehension, use and misuse of product, and with an emphasis on persons

under the age of 26.

FDA has met with multiple tobacco manufacturers about dissolvable tobacco products. Confidential commercial information was presented. It will not be presented in an open meeting to the public. However, it will be used to inform FDA decision making.

I'd now like to move on to FDA's research activities. FDA will be conducting consumer perception research. Our objectives are to better understand consumer perceptions, beliefs, awareness, and behaviors around dissolvable tobacco products and advertising, and to inform future quantitative research and communications around dissolvable tobacco products.

The design includes individual interviews and focus groups. The cities include Portland,
Oregon; Columbus, Ohio; and, Charlotte, North
Carolina. And FDA plans to summarize this information and present it at a future TPSAC meeting.

The FDA is also working with CDC and its

tobacco laboratory to perform a standard quantitative analysis on pH, nicotine, tobaccospecific nitrosamines and flavors, and the FDA will be presenting this information at a future TPSAC meeting.

Now, I'd like to move on to other FDA activities. FDA has requested information on dissolvable tobacco products from poison control centers, including reports on adverse events. We have reached out to other countries to understand the regulation in their countries, product availability of dissolvable tobacco products, marketing, and health effects. And we recently reached out to the states to understand the prevalence of dissolvable tobacco product use in states, including any survey data, poisonings or adverse events, consumer perceptions and marketing strategies, as well as educational or awareness campaigns that may have been carried out on a state or local level.

FDA issued letters to manufacturers on June 10th, 2011. Manufacturers are required to

submit documents and information relating to research conducted, supported or possessed by the manufacturers or its agents relating to specific topics.

This information is required from industry, all documents and underlying scientific information relating to research and research findings on the following topics: marketing research involving the use of dissolvable tobacco products; marketing practices and the effectiveness of marketing practices used by tobacco manufacturers and distributors; the health effects, toxicological effects, behavioral effects, and physiologic effects of dissolvable tobacco products.

FDA requested voluntary submission of additional information to provide context and background for TPSAC. This includes a complete description of the composition and design of each dissolvable tobacco product, a brief summary of the process, criteria and considerations utilized in selecting the form, flavoring, and sugar content of each dissolvable tobacco product; marketing

research on the use of dissolvable tobacco products by age, type of prior tobacco use and by interest in quitting cigarette smoking or traditional smokeless tobacco use. This includes consumer perceptions of taste, impact, nicotine strength, and product harm.

We also asked for marketing practices and the effectiveness of marketing practices by age, type of prior to tobacco use and by interest in quitting cigarette smoking or traditional smokeless tobacco use.

short summaries of the health and toxicological effects of dissolvable tobacco products; behavioral effects of dissolvable tobacco products among users and non-users of other tobacco products regarding appeal, use, initiation, cessation, switching between cigarettes and dissolvable tobacco products, switching between traditional smokeless and dissolvable tobacco products, and dual use of cigarettes and dissolvable tobacco products. We asked the companies to summarize these results for

users of different ages.

Finally, we asked for physiological effects of dissolvable tobacco products on users and non-users of other tobacco products, including, but not limited to, chemosensory effects and abuse liability.

This information is due to FDA by

August 1st, 2011, and we do intend to summarize

this information and present it at a future TPSAC

meeting.

With that, I'd like to focus now on the questions to TPSAC.

In response to the information you have been provided for this meeting, discuss the possible public health impact relating to marketing of dissolvable tobacco products, perception and use of dissolvable tobacco products by children and adults, abuse liability, health risk, and risk of accidental ingestion of dissolvable tobacco products tobacco products, features of dissolvable tobacco products that may contribute to tobacco initiation, and features of dissolvable tobacco products that may

leads tobacco users to singular or dual use of 1 dissolvable tobacco products instead of quitting. 2 Additional questions for TPSAC to consider 3 4 today are what additional topics, if any, would you like FDA to ask the tobacco industry to present at 5 the next TPSAC meeting, and are you aware of any 6 available information or research that you would 7 like FDA to request to be presented to TPSAC to 8 help inform the report and recommendations on 9 dissolvable tobacco products. 10 11 With that, I'd be happy to answer any 12 questions. 13 DR. SAMET: Thank you. I think, actually, I 14 have a couple questions that you can answer. DR. EVANS: Sure. 15 16 DR. SAMET: I think our next meeting is November 2nd and 3rd, so just let everyone fix that 17 18 date in their mind. And our report will be due March 23rd, 2012. So just think about for sort of 19 our working schedule. 20 21 I did want to ask, you mentioned the consumer perception research and your laboratory 22

analyses and said they would be available at a 1 future TPSAC meeting. 2 Give us an idea of which future TPSAC? 3 4 DR. EVANS: We anticipate the information due at the end of September, which means, ideally, 5 we would like to present it at the next meeting, 6 but I cannot promise that at this time. 7 DR. SAMET: Okay. 8 DR. EVANS: But it's coming. 9 DR. SAMET: Okay. Before we move on both to 10 11 these questions and I think perhaps a more general discussion, I want to see if there are clarifying 12 questions. 13 DR. LAUTERBACH: Dr. Evans, how come one of 14 the charges to the committee is not to look at the 15 16 benefit of using dissolvable tobacco products in terms of individual health, public health, versus 17 18 use of much more hazardous tobacco products? 19 DR. EVANS: I believe, as Dr. Ashley mentioned yesterday, we have a workshop coming up 20 21 in August to address those issues. 22 Actually, John, I would construe DR. SAMET:

1 public health impact rather broadly. I don't think it implies the directionality of either adverse or 2 non-adversity. It's open. It says "impact." 3 4 think any possibility is certainly on the table to look at with that definition. 5 David? 6 DR. ASHLEY: That's exactly right. 7 developing that question, that is exactly what we 8 intended it to mean, not just adverse effects of 9 dissolvables but positive effects of dissolvables. 10 11 DR. SAMET: Mirjana? DR. DJORDJEVIC: You said that you're 12 planning to do quantitative analysis at CDC. Are 13 you going to do anything else beyond what you 14 presented in the list, like expressing the level of 15 16 free nicotine, heavy metals, pH, maybe radioactivity? 17 18 DR. EVANS: I can tell you today I'm only speaking on an overview of the activities and not 19 specifics, but we will take that under 20

Thank you.

consideration.

DR. DJORDJEVIC:

21

22

DR. SAMET: Bob? 1 DR. BALSTER: Did you decide which companies 2 were marketing dissolvable products or did you let 3 4 them decide which companies were marketing dissolvables, per your request? 5 DR. EVANS: We have taken a broad overview 6 of the definition of dissolvable tobacco products, 7 and we're looking forward to discussion from TPSAC 8 to help us refine that view. 9 DR. BALSTER: I mean the fact that we didn't 10 have presentations yesterday, for example, on snus. 11 Some people have defined that as a dissolvable 12 product. I'm not saying that I think it should or 13 shouldn't, but none of that information was 14 available yesterday. Although there was a lot of 15 information about snus products presented here, the 16 manufacturers of them weren't here. 17 18 How did that come about? Was that a 19 decision you made not to inquire from them, or did they simply not self-define as making dissolvables? 20 21 What was the story there?

I think I'm going to let David

DR. EVANS:

22

answer that question.

DR. ASHLEY: When we were thinking about dissolvable products, we were looking at what we believed were dissolvable products. And as Sarah said, we really are counting on some input from TPSAC to help us refine the concept of what we think or what may be dissolvable products. And so we're looking for input from you guys.

Again, this was our first thought on it, what we believed it to be. We were certainly not intending to be exclusive or to prevent someone else, but tried to come up with what we would think would be a dissolvable; though, again, we don't have a definition right now. There is no statutory definition, and so we would appreciate what -- the discussion that occurs here, how that might help inform our own progress in moving forward.

DR. BALSTER: My view on this is that I don't know either exactly what should logically be defined as a dissolvable product. But because so much of the science of what was being shown yesterday and what we know to be relevant is coming

from the snus experience, I would think having the 1 snus data for us, even short of including them in 2 the definition or not, seems like a very important 3 4 and relevant comparator. And I don't know if you have the authority to get that sort of information 5 on that class of products. 6 DR. SAMET: I think we ought to continue our 7 discussion. Again, part of what we need to do 8 today is determine what additional information we 9 want. And I think yesterday we heard a lot about 10 smokeless, and, remember, my concluding comment was 11 we have to think about the utility of those data. 12 Neal? 13 DR. BENOWITZ: Are we going to talk about 14 this later? I was going to respond to Bob, but if 15 16 we're going to talk about this later --. DR. SAMET: I think we're going to have the 17 18 general discussion. So let's just address 19 clarifying questions related to the presentation

I had one additional question.

DR. EVANS: Sure.

from Sarah.

20

21

22

DR. SAMET: You said there were 1 international inquiries. I guess my question would 2 be to whom and are there analogous products on the 3 4 market outside of the --DR. EVANS: Right. And we will be reporting 5 on that. I can give you the full list. I can tell 6 you we have countries like Canada and Brazil. 7 at this time, we're only aware of a dissolvable 8 tobacco products by R.J. Reynolds in Taiwan, but 9 we're still waiting for information from that 10 11 country about it. Mark, do you have questions? 12 DR. SAMET: DR. CLANTON: My principal concern about 13 this topic would be the safety and concern for 14 ingestion and poisoning of children. So I will 15 really look forward to seeing the data presented 16 from poison centers, as well as from other 17 18 countries as it relates to the possibility of 19 accidental poisoning. So that's what I'm looking forward to. 20 21 DR. SAMET: Okay. 22 Anything else, clarifying questions in

relationship to the presentation we just heard?
[No response.]

Committee Discussion

DR. SAMET: Okay. Thank you.

So if you look at the agenda, it now says committee discussion, and we have a lot of time for committee discussion. And I think we need to look, I think, carefully at a couple of things. One, are there specific types of data that we want to hear about at the next meeting, the example of snus? Further information on snus was raised by Bob.

For example, we have these questions laid out in this slide number 19, which essentially is a lengthy list of items, and I think that we should spend some time thinking about how we're going to frame our approach to the problem of dissolvables, dissolvable tobacco products.

Thinking back to our discussions essentially a year ago when we talked about how to approach menthol and ended up, among other things, framing our discussions around this conceptual diagram and model that, in fact, became, in part, the basis for

the model that David Mendez carried out, just as a reminder, when we did that, we looked at public health impact as representing the consequences of the availability of menthol cigarettes versus a counterfactual, to use that word again, of a world had there never been menthol cigarettes.

I think, at this point, possible public health impact, because we're looking here to the future instead of, in part, to an experience that was already played out with the availability of menthol cigarettes.

So there are differences, but I think we're left with discussing what we mean by public health impact in this context, and, as John has already reminded us, allowing for the possibility of adverse consequences of the availability of dissolvables and beneficial consequences of the availability of dissolvables.

Just one further thought that has already come up. We heard a fair amount about harm reduction yesterday and the possibility that having these products in the marketplace would reduce use

of cigarettes and that there could be beneficial consequences there. That said, our task is not to address harm reduction in general. It's the public health impact of dissolvables. So how we're going to find the line here, I think, is something else that we should discuss.

I recognize these are all difficult issues, but we're going to have to take them on, and we might as well start feeling our way through them.

I do think it would be useful to revisit some of the discussion that we had at the start of the menthol work. And at that point, as I recall, I wrote a note sort of setting out some of these issues in I think sort of the first version of the diagram. So I would encourage our new members to read the menthol report; in particular, look at how we approached the problem, because I think there's some useful thinking there.

Then as we heard, the literature review identified only 22 articles, and probably we've all looked through them now, and there's not too much evidence available, yet, directly on dissolvables.

So we'll also face the challenge of saying, well, what about all the lessons from other types of smokeless products and do they work here.

So I'm just sort of setting out some of the,
I think, more difficult issues that we're going to
have to probe as we approach this problem.

So let me throw the floor open for discussion. And I think we have sufficient time to talk. Then we'll take a break and then move on to the public hearing, and then we have an opportunity after the public hearing, the public comments, to return and reflect again, based on what we've heard.

DR. NEZ HENDERSON: I think the challenge with this topic is just the amount of time these products have been on the market. So we don't really have too much history like we did with menthol cigarettes. So I guess that's my big concern, is how do we approach this, with just 22 peer-reviewed literature and where do we go from there.

DR. SAMET: Fred?

DR. PAMPEL: One way to get more information is to find out more about Sweden. The data were reported, but I understand there's some controversy over to what extent snus was responsible for the drop in male smoking or polices. There are published articles, but it might be helpful to try and get more information on the latest trends or some unpublished information. It's not exactly a counterfactual, but it provides information that we won't get from the United States alone.

DR. SAMET: Okay. And just on the snus situation, we did see some of the data yesterday. I think it must have been about three or four years ago I had reviewed that literature. I think an updating would be useful. I think the story is complicated, and I think we would have to look at it closely ourselves to decide, again, is there a lesson there that we would bring into our consideration of dissolvables.

So we can come back to this. So possibly more on snus may be something we want to hear at

the next meeting. And, also, I think we would need to have that literature looked at by our group.

Neal?

DR. BENOWITZ: The first comment with relation to snus, snus and the dissolvables we've heard about are really totally different products with respect to nicotine delivery, which would have a huge impact on how they're used.

Snus basically delivers daily doses of nicotine comparable to cigarette smoking. Many studies have shown that. These dissolvables generate levels that are really, really low. So I don't think that we could look at population use of snus and understand dissolvables, because nicotine kinetics and dosimetery are just totally different. There are some general principles that I think are worthwhile looking at, but I do not think we can extrapolate data from the Swedish use of snus to these products.

The second general comment is, one of the tricky things is impact may depend on marketing, and marketing depends, in part, on what the FDA

says the product can be marketed as. So there's a little bit of confounding here.

If they can all be marketed for smokers when they can't smoke, that's one thing. If it's decided that these products are going to be marketed for harm reduction, that's a different impact. And I don't know how to address this question, but I think it's something we need to keep in mind.

DR. SAMET: Bob?

DR. BALSTER: I had a question for Neal. So if you were to take a distribution of, let's just say, blood levels of nicotine after using dissolvables and various snus and you were to plot them out -- I mean, it would be clearly two, a bimodal distribution. There's no kind of land in between where there are low level snus and high level, quote, "dissolvables."

You're implying that the nicotine levels are so different that they represent different distributions. Is that really true?

DR. BENOWITZ: Well, it doesn't have to be

true, but the products that we were provided data on generate nicotine levels of maybe 3 to 5 nanograms per ml with a single product. If you take 3 of -- I forget which product -- you might get up to 7.

Snus generates levels that are like cigarette smoking, and the amount of nicotine in a dose of snus is much higher than nicotine in a tablet, at least the ones we looked at. Now, dissolvables could be made differently. They could be made like snus. But the products we've seen so far would be a different distribution.

DR. BALSTER: I guess I would just say on that, again, I agree perfectly where the nicotine delivery or nicotine content would be an extremely important determinant of how the products would be similar and different. But, ultimately, if you look forward over time, all of these things can change in every direction, and we could get weaker snus and stronger dissolvables.

I mean, just the idea that we can at this moment in time capture the situation, where if

we're looking at relatively low nicotine delivery 1 dissolvable products, is that going to serve us 2 well if we think about this over this, like, 3 4 10-year run? DR. BENOWITZ: I think it's a great point. 5 And one question is, would FDA want to define 6 somehow the nicotine content of products as related 7 to risk or related to harm reduction, or whatever, 8 because these products are low nicotine. 9 you're right. It could be as a much higher 10 11 product. And so if FDA says one thing about these products, is that true for a higher nicotine 12 product? I think that's a great question. 13 We'll come back maybe and ask 14 DR. SAMET: David and Sarah to respond. 15 16 Karen? MS. DELEEUW: Yes. We heard yesterday that 17 18 these products can't be advertised for harm And to the extent that there was some 19 reduction. rationale behind that thinking, I think it would be 20 useful to understand how that decision was made. 21

David, do you want to just

DR. SAMET:

22

remind everyone about the process? Should there be a harm reduction claim?

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

I don't recall. DR. ASHLEY: I'll have to think about it a little bit, whether the terms "harm reduction" actually are found in the statute So I'm not going to deal with the term "harm reduction." We'll deal with the term "modified risk," which is the term that's used in the statute. And there are specific requirements for FDA -- there are specific requirements if a company wants to come to FDA desiring to make a modified risk claim and the information they need to produce, and there's also very specific information about how FDA will make a determination of whether a product is modified risk. And that's laid out fairly carefully in the statute.

To date -- I think I can say this -- FDA has received some modified risk applications. I'm not going to say what they are or what they're about.

FDA has acted on those applications, and FDA will continue to act on those applications as they come in.

So there are specific details on modified risk that are laid out in the statute, including what the companies must deliver and the determination, how FDA is supposed to base their determination.

DR. SAMET: Dan?

DR. HECK: I think, to Neal's comment about the levels of nicotine in at least the early generations of products we've seen to date, I think it would be interesting to see, when we do get some more real-world consumer information, whether consumers may choose to use one or two of these sticks or two or three of these dissolvable Orbs as a matter of routine.

DR. SAMET: Other general questions? Again, we're responding right now to the presentation we heard.

DR. BALSTER: I guess this would be in the category of a general question. I think one of the key areas in which we need to get real clear is what is the role, if any, in the use of these products for initiation of tobacco consumption.

That's sort of a key component of this.

We heard presentations on this, and I've read a little bit. And, to be honest, I don't really feel like I have anything like a clear picture on that yet. A lot of them, of course, we're including different products as potential initiators, like a lot of them were just smokeless tobacco.

I remember seeing one of the presentations that was saying initiation rates -- current smokers who initiated on smokeless tobacco, it might have been as high as 30 percent, and they were saying, well, that's not very many. Well, that's actually, in my way of thinking, an awful lot.

So I don't know whether there's anybody that we could identify that is really an expert on sort of the initiation with non-smokable products who could come and make some presentations to us or something. That whole issue, to me, as I listened to the presentations and read, I feel like I really don't have a handle on that. Maybe I'm the only one who doesn't have a firm grasp of what I think

that situation is.

DR. SAMET: I suspect we're all in the same realm of uncertainty here.

Mark, do you have anything you want to say at this point?

DR. CLANTON: I do. I agree that there's a lot we don't know about this particular product, but there is an elephant in the room that we need to pay attention to. And that elephant is hypertension, which is a large-scale problem in this society. It happens to be a particular problem in the marketed demographic of this product, and nicotine absolutely has an effect on blood pressure. And it has an effect of increasing blood pressure in people who have hypertension.

So I think it's going to be important to certainly gather what information we can, but, also, plan to prospectively measure things like hypertension, stroke and heart attack in people who will eventually be taking this product, potentially in a phase 4 kind of model.

But I want to make it very clear,

hypertension and the potential impact of the 1 product on hypertension is very important to pay 2 attention to. 3 4 DR. SAMET: Neal? I think in response to Mark's 5 DR. BENOWITZ: comments, this is where snus could be useful, 6 because there are a lot of data on cardiovascular 7 effects. The Heart Association review, which was 8 part of our packet, looked extensively at this. 9 And if you say that snus provides people with much 10 more nicotine than these products, you can at least 11 say that these products would be as or less toxic 12 than snus. 13 So I do think we have a lot of data based on 14 the snus for hypertension and cardiovascular 15 16 disease. DR. SAMET: Other thoughts? 17 18 [No response.] 19 DR. SAMET: So I just want to go back again to menthol for a moment. So if you'll remember, 20 menthol, we ended up with a model, this diagram, 21 22 that began with experimentation and initiation to

the left side and ended with premature death to the right as an indicator, and if we at least thought through the ways that we might organize our thinking about the potential public health impact.

We heard from, I guess, Bob's discussion about role in initiation and would there be one and their experience with other smokeless products potentially useful, and we would want to think about whether they would have any role in the trajectory of smoking in youth, potentially -- I mean, here, we're obviously going to be moving into a realm with essentially no information.

We would be -- again, if we sort of proceeded from left to right in that diagram, we would want to think about cessation and whether the impact could be to reduce rates of cessation, because, for example, the situation of smoke-free environments that might promote cessation would now be a circumstance where a dissolvable would provide a tobacco product or perhaps they would increase the likelihood of cessation. Again, we'll leave that open and that would be a question we would

need to explore.

There would be also this question of potential dangers to health and how any particular use pattern of these dissolvables might contrast to either continuing to smoke cigarettes or to quitting. I think those are the two opposite states.

Then the other consequence that is on the table that we've heard a lot about is ingestion as an adverse consequence. And just sort of organizing ourselves, we would like to have information about these different, I think, important conceptual points.

We know that there's not going to be very much available for dissolvables, per se. The question of what we can bring in from other products we'll need to think through. And for ingestion, there may be some empirical data. We'll have to see how much is available.

So this would leave me thinking that we're going to have to explore some aspects of the smokeless literature, in general, in some depth,

and we may want to think about how we're going to approach that.

If we did have some sort of general framework following on menthol, at least it would highlight for us what we need to be thinking about and where the data gaps are that FDA, as it continues, will need to fill and track, because, clearly, there's going to be a lot of uncertainty.

So I think we need to get something like this down on paper so we can have it for discussion for writing. And, again, we'll go back and refresh my memory, but I think that I produced such a note for menthol.

So other comments? John?

DR. LAUTERBACH: Dr. Samet, you mentioned ingestion. Are you looking at adult ingestion or the pediatric ingestion, or both?

DR. SAMET: Well, so far, of course, John, all the discussion has been about inadvertent pediatric ingestion.

Are you suggesting that adults will also ingest this?

DR. LAUTERBACH: Well, obviously, 1 dissolvables have to go someplace, Dr. Samet. 2 DR. SAMET: Yes. 3 4 [Laughter.] DR. LAUTERBACH: No. But, I mean, are we 5 going to look at -- by ingestion, are we concerned 6 with the accidental poisonings? 7 DR. SAMET: Accidental poisoning, yes. 8 Thank you for the clarification about the GI tract. 9 [Laughter.] 10 DR. SAMET: Other comments? Patricia? 11 DR. NEZ HENDERSON: Is there any national 12 data on youth initiation, or is that something that 13 is going to be requested? 14 15 DR. SAMET: I think this goes back to, I think, Bob's comments, as well. I think we'll have 16 to explore what is there for smokeless, in general, 17 18 and I think, obviously, the most contemporary data. I think, one other point, I think Neal 19 brought up the importance of marketing and what it 20 might look like and, again, how that could, in 21 22 this -- whatever theoretical scenarios we have to

think through for public health impact, we'll have to think through what the marketing might look like.

Any other -- yes? Dan?

DR. HECK: Just a small comment. I know on this initiation topic -- and I think, in a sense, already there's probably not going to be a lot of useful information yet. But our difficulty is going to be trying to discriminate, let's say, an adolescent who initiates with one of these novel products, to discriminate the people who wouldn't have initiated any tobacco use otherwise from those who otherwise would have initiated smoking.

I know this very sophisticated model we saw

Geoff Curtin present yesterday -- I guess we all

saw it simultaneously for the first time. It's a

little daunting in its complexity, but it seemed

like something like that, a tool like that

may -- where data is thin, may enable us at least

to get a sense, if we can bring this to

application, of discriminating those numbers

from -- perhaps a certain percentage of the

initiators are diverted from smoking careers from the outset by such products.

DR. SAMET: Okay. I'm going to suggest that we might take a brief break and then come back and do the public hearing. And then I think after we've had the public hearing, that we could then, I think, make perhaps -- make a list of some of the points we want to follow up on, and I think get a little more specific.

I can appreciate why we're not bubbling with ideas. There's an awful lot of uncertainty here, and I think it would be useful, though, to make a very specific list perhaps organized around the kind of rough framework I was talking about.

Neal?

DR. BENOWITZ: I was just wondering. Are we going to be actually addressing these items A through G today? Are we talking about our initial impressions on these today?

DR. SAMET: I think we should probably be thinking about what information we need to really begin to address them. I mean, we've heard a range

1 of -- we heard several presentations yesterday from I think, to me, our discussion at this 2 industry. point should be more about what we need to begin to 3 4 provide answers to those questions. DR. BENOWITZ: Okay. So we can go through 5 each one not to answer it, but to say what 6 information do we need to address it. 7 DR. SAMET: Right, right, right. 8 don't -- again, these are discussion questions. 9 These are not answer questions yet. I think there 10 will be issues that we need to take on as we move 11 12 through our report. So we will take a premature break and 13 reconvene at 9:00 for the open public hearing. 14 (Whereupon, a recess was taken.) 15 16 Open Public Hearing DR. SAMET: Welcome back, and we'll now 17 18 continue with the open public hearing. We have five speakers, each with 10 minutes each. 19 Both the Food and Drug Administration, FDA, 20 and the public believe in a transparent process for 21 information-gathering and decision making. 22

ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor and its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The

insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Then just as a reminder, each speaker will have 10 minutes, and you will have a warning light on the podium.

So we'll begin with our first public speaker, Elaine Keller, from the Consumer Advocates for Smoke-free Alternatives Association.

Ms. Keller?

Speaker Presentation - Elaine Keller

Ms. Keller: As you've already been told,

I'm Elaine Keller, and I'm the vice president of
the Consumer Advocates for Smoke-free Alternatives

Association. I have no conflicts of interest to declare.

Our organization was formed by thousands of people who struggled for years to stop smoking.

Many of us had given up all hope, when, to our surprise and great joy, we were able to quit by switching to less hazardous alternative sources of nicotine. Our mission is to save the lives of other smokers. We work to provide the public with truthful information about effective, affordable, reduced-harm alternatives.

The current approach to smoking cessation is based on nicotine abstinence. Nicotine abstinence is not the only way or even the most effective way to stop smoking. Insisting on abstinence creates a roadblock to smoking cessation.

The Royal College of Physicians' 2007 report pointed out that nicotine abstinence is unworkable for some smokers, especially those who are self-medicating underlying conditions that impair their cognitive and/or emotional health. The practice of tobacco harm reduction, offering less hazardous

alternative for smoking, could save millions of lives.

Congress recognized the importance of offering less hazardous alternatives; hence, the existence of Section 911. This table provides a comparison of the daily TSNA exposure from a variety of products, expressed in micrograms.

The TSNA content of the 16-milligram electronic cigarette cartridge was reported by Dr. Murray Laugesen of Health New Zealand, and the remaining product values came from the article, Tobacco-Specific Nitrosamines in New Tobacco Products. The daily dose values came from an Internet search of what the average intake might be, and the last column is the result of multiplying those values.

The important thing to note from this is that all of the smoke-free alternatives result in a daily exposure of 16 micrograms or less. Since Swedish Snus users have about the same cancer risk as former smokers who gave up all use of tobacco, it seems likely that switching to any of the smoke-

free products would reduce cancer risks for smokers.

It's obvious that smoking exposes the user to many more hazardous substances than smoke-free alternatives. Both types of products, smoked and smoke-free, contain nicotine. How hazardous is nicotine to health?

Dr. Neal Benowitz is one of the world's leading experts on nicotine safety and toxicity. He presented this information at the FDA workshop last fall on long-term use of NRTs.

We have data on decades of long-term use of reduced nitrosamine snus. Smokers switching to snus enjoy significant health improvements and live just as long as smokers who stopped using all forms of nicotine. And recent population surveys show that over 90 percent of smokers who switch to e-cigarettes report that their health has improved.

This makes sense when you stop to consider that all of the lung damaging components of cigarette smoke are eliminated with these alternatives. Based on the data from these other

products, there is good reason to believe that smokers who switch to dissolvable tobacco products will experience improvements in their health, as well.

CASAA endorses three classes of alternatives: smokeless, electronic cigarettes, and pharmaceutical nicotine products. However, NRT products require some changes to become more effective. More smokers would make the switch if higher nicotine doses were available and if longterm use wasn't discouraged.

Moore, et al. found that when used as directed to wean down and off nicotine, the NRT success rate is only 7 percent at six months,

5 percent at 12 months, 2 percent at 20 months. We need to ask ourselves is this acceptable. Why all the concern about nicotine abstinence when it's the smoke that kills?

Long-term use of nicotine gum results in better smoking cessation rates than weaning off nicotine. Lund, et al. looked at seven Norwegian cross-sectional studies that compared smoking quit

rates of snus users to never users of snus. In every case, a higher percentage of snus users had quit smoking. Population surveys also show much higher smoking cessation rates from switching to e-cigarettes than the usual nicotine abstinence approach.

Opponents of tobacco harm reduction have done their best to convince the public that dissolvable tobacco products are highly dangerous.

Let's look at the evidence for each of these.

There is zero evidence that using dissolvable tobaccos increases the risk for oral cancer or any other type of cancer. Peter Lee summarized the epidemiological evidence relating to snus to health and found that using snus reduces the risks of all types of cancers compared to continued smoking.

So how could switching from smoking to products that reduce TSNA exposure even further than snus increase oral cancer risk?

Again, there is zero evidence that using dissolvable tobacco serves as a gateway to smoking.

In fact, the opposite is true. In Swedish men,
92 percent of primary smokers who later used snus
quit smoking. Over time, snus apparently makes it
possible for many more smokers to quit. In the
USA, 73 percent of the most recent quit attempts
using smokeless were successful.

If uptake in the U.S. has been slower than in Sweden, perhaps our government-required warning labels have something to do with it. Labels that claim the product is not a safe alternative endangers the health of current smokers by implying there is no benefit in switching from smoking to a smoke-free alternative. Even worse, those labels convince youngsters that there's no increased risk in switching to smoking. We need to provide accurate health information to the public.

Dr. Gregory Connolly examined data on 13,705 tobacco product poisoning cases and found only one case caused by a dissolvable tobacco product. As you can see, cigarettes is the number one and nicotine pharmaceuticals come in number three. All nicotine products need to be kept out of the reach

of children and pets and should be offered in child-proof packaging.

Marketed to children? Well, anyone who has such evidence should contact their state attorney general because this would violate the 1998 master settlement agreement. To avoid encouraging children to try these products, perhaps the tobacco control community should refrain from calling them "tobacco candy." Dissolvable tobacco products come in flavors such as mellow mint and java. Is this evidence that the products are marketed to children?

This is a mailer that I received from CVS Drugstores. Obviously, GlaxoSmithKline recognizes that adults want their nicotine served up in pleasant flavors.

Dissolvable tobacco products reduce
exposure, and it's reasonably likely that they're
going to reduce morbidity and mortality. This
should not be about politics or profits. People's
lives depend on a change in attitude, education,

and product availability. The public needs 1 accurate information about nicotine. There's no 2 evidence whatsoever that dissolvables cause gum 3 4 disease, tooth loss, or any type of cancer. remove these warnings. 5 If something must be said about comparative 6 safety to smoking, let's provide a more accurate 7 message. It's time to start educating smokers 8 about the health benefits they can realize by 9 switching to less hazardous alternatives. 10 time to stop focusing so hard on nicotine 11 abstinence that we lose sight of the goal of saving 12 lives. 13 As Nigel Gray and Jack Henningfield pointed 14 out, acceptance of the status quo is disastrous. 15 16 Failure to act under these circumstances is negligence. 17 18 DR. SAMET: Thank you. Are there questions for our speaker? 19 Mark? DR. CLANTON: No questions. 20 21 DR. SAMET: Okay. Very good. Thank you

very much for your presentation.

22

Thank you. 1 MS. KELLER: Sorry. We're just putting up 2 DR. SAMET: the timer. Thanks for being on time absent the 3 4 timer. [Laughter.] 5 DR. SAMET: Give Tom a moment here. 6 [Pause.] 7 DR. SAMET: Our next presenter is Wallace 8 Pickworth from Battelle. 9 Speaker Presentation - Wallace Pickworth 10 Thank you for the 11 DR. PICKWORTH: opportunity to address the discussion of 12 dissolvable tobacco products. My name is Wallace 13 Pickworth. I am a research science leader at 14 15 Battelle Memorial Institute and director of its 16 human exposure assessment laboratory in Baltimore. Battelle has decades of experience in 17 18 testing the composition, design and toxicity of tobacco products. My recent experience with 19 tobacco and nicotine began during my career as a 20 scientist at the National Institute on Drug Abuse, 21

where I led studies determining the abuse liability

22

and addiction potential of many classes of drugs, including combustible and oral tobacco products.

Today's comments concern Battelle's recommendations for research on dissolvable tobacco products. Although there is a need for a wide breadth of research on these products, I am confining my recommendations to the addiction potential posed by dissolvable tobacco products.

The International Association of Research on Cancer and other organizations recognize the importance of addiction and considering addiction in assessing cancer potential because they recognize that addiction leads to continued use of these products in spite of imminent and recognized harm.

The addiction potential of tobacco products is directly related to the amount and speed of nicotine delivery to the brain. This conceptualization explains why cigarettes, which provide immediate delivery of nicotine into the blood stream, are more addictive than the nicotine patch, which provides very slow absorption.

To provide relevant data for the regulation of dissolvable tobacco products, we propose a series of pharmacokinetic and pharmacodynamic studies comparing dissolvable tobacco products with other oral products, such as moist snuff and chewing tobacco, and pharmaceutical products, such as the nicotine gum or the Commit lozenge.

Pharmacokinetic studies assess the amount and speed of nicotine absorption and elimination from the blood. They also test the influence of other factors, such as flavorings and pH, on the absorption and elimination.

For example, at NIDA, we showed that the bioavailability from nicotine gum was seriously decreased by acidic beverages such as coffee or soda. In other studies, we demonstrated that the nicotine absorption from moist snuff was increased with increased pH of the product. Increasing the pH results in a higher percentage of nicotine in the freebase form. The freebase configuration is more readily absorbed into the bloodstream and onto brain nicotine receptors.

At Battelle, we are currently conducting an NCI-funded pharmacokinetic study on the influence of pH and menthol and wintergreen flavorings on the uptake of nicotine from moist snuff. This experimental paradigm could be used to test dissolvable products, as well.

Pharmacodynamic activity can be measured from both physiologic and subjective responses.

The subjective evidence of the participant is fundamental to another determinant of abuse liability, product liking. So product liking is assessed by asking questions about perceptions of appeal, strength, alertness, arousal, head rush, mitigation of tobacco withdrawal, and other psychoactive effects. These responses are quantified by means of visual analog scales.

It is my hope that the FDA will develop and support mechanisms for directly funding studies designed to provide information to answer questions relevant to tobacco product regulation. This would benefit both the FDA and the researchers who want to provide data responsive to regulatory needs.

Specific to dissolvable tobacco products, there is a need for more clinical information and assessment of appeal, especially in women and youth.

In summary, the addiction potential of dissolvable products is unknown. Comparisons of pharmacokinetic and pharmacodynamic effects of the products are needed to place them in the continuum of addiction potential among other oral and combustible tobacco products and pharmaceutical nicotine. These studies will provide science-based assessment of their abuse potential and inform regulatory decisions.

Thank you.

DR. SAMET: Thank you. Questions? Neal?

DR. BENOWITZ: Wally, in our docket, there
were a number of papers that looked at the
pharmacokinetics of single doses of these products.
First is snus products and cigarettes, and looked
at heart rate responses, subjective responses.

Are there other things that you think should be done that are not done already? Because we saw at least five or six papers that have looked at

that, the straightforward kinetic-dynamic issues. 1 Are there some things you think should be 2 done that have not already been done? 3 4 DR. PICKWORTH: Well, I think we need dose-response studies. I think we need studies 5 that look at the influence of the flavoring agents 6 that are added to the dissolvable products. 7 It's our theory, and we're testing this in 8 studies right now, that, for example, menthol, 9 which increases blood flow, diminishes membrane 10 11 permeability and increases salivation, will all interact with, say, pH, for example, to increase 12 the nicotine absorption. 13 So I would say there are probably 14 interaction studies that need to be done and 15 16 probably larger dose-ranging studies, as a minimum. DR. BENOWITZ: Thanks. 17 18 DR. SAMET: Bob? 19 DR. BALSTER: Wallace, one of the things that we discussed briefly here that's sort of 20 somewhat of a unique challenge for these various 21 22 dissolvable products -- of course, they're coming

in different forms, pill-like things and sticks and things -- but is that their placement in the mouth and the way in which they're actually used probably influences their absorption characteristics; so if it's left on the gum, I imagine, if it's put in the mouth, if it's chewed, if it's swallowed.

What would your estimate be about the variability that one would encounter, depending upon different kind of forms in which people might use the products?

DR. PICKWORTH: Well, I can't speak specifically to the dissolvables, but in our studies with the moist snuff, we found that people were very idiosyncratic. They always put the product in the same spot in their mouth almost every time they used it, even if there were lesions in their mouth at that point or recessions of the gum or other pathology. That is exactly where they continued to put it.

So I think that that bears on that. I think it depends on whether it's an experienced user that's had a lot of experience and possible

pathology, a person that's used, for example, moist 1 snuff before they used dissolvables, or a person 2 that is first-time use. 3 4 So I think there would be variability, but I think within a person, I think it would -- my guess 5 is it would tend to vary out. 6 DR. SAMET: Other questions? Mark? 7 I'm sorry, John. Go ahead, John. 8 DR. LAUTERBACH: Dr. Pickworth, in your 9 studies that include NRT, have you seen any 10 difference in any of your measures between highly 11 flavored NRTs, including those that have menthol on 12 the ingredients, versus unflavored? 13 DR. PICKWORTH: I didn't do the studies with 14 the flavoring on the NRT. Those were done at Johns 15 16 Hopkins by Al Hirschmuller. And my understanding of it was that the menthol did not increase the 17 18 liking of the product compared to the unflavored product. 19 DR. SAMET: Mark, sorry. I think I lost you 20 21 there. Did you have any questions? 22 DR. SAMET: Go ahead.

DR. CLANTON: I do. My question has to do with -- it looks like there's a tremendous amount of research on the metabolism of nicotine in the body. However, sort of where the rubber meets the road is at the nicotinic acetylcholine receptor in the brain.

Clearly, not everybody is affected psychologically the same way by the same dose of nicotine, and there are probably receptor polymorphisms that cause some people to have high affinity and hold onto small doses of nicotine for a long period of time and others who probably need to have that nicotine replenished on a frequent basis.

What kind of research is going on as it relates to nicotinic receptors and sort of polymorphisms and differences in populations as it relates to those receptors?

DR. PICKWORTH: Well, most of the research on the neuroscience has been done in animals, and the research that has been done in people is largely with cigarette smoking.

One of the neuroscience findings of people that continue to take nicotine is they have an increase in the number of receptors. There's also the issue of the sensitization and desensitization of the product; that is, the effect of the product seems to be more evident during the ascending part of the dose response curves, whereas even if the blood levels are sustained, the effect goes away, if you look at, say, something like heart rate or head rush. So the blood levels will stay up while the effect diminishes, and this is thought to be due to some immediate desensitization.

The fact is that I don't know of too many studies in animals, and none in people, where people have looked at up-regulations of receptors, desensitization, using oral and specifically not dissolvable tobacco products.

We are, in the current study, looking at the effects of metabolism; that is, you can find polymorphisms in nicotine metabolism. Some people rapidly metabolize -- or more rapidly metabolize it than others. So we are seeing whether or not that

makes differences in the moist snuff study that we're doing now.

DR. SAMET: Neal, I was going to ask if you wanted to comment further.

DR. BENOWITZ: No. I wasn't going to comment on that. I just wanted to ask, again, in the docket, in the papers that we saw, there were several papers from Tom Eissenberg's group and Dr. Hatsukami's group that looked at liking, and the dissolvable products were not liked very much in comparison to sticks.

Do you think that that's a good answer in terms of abuse liability or do you think more studies need to be done on abuse liability, given the fact that the studies so far don't suggest that people like these products very much?

DR. PICKWORTH: As I say, and similar to the answer I gave before, there's probably a vast variety of responses. I think that one of them you have to consider is how much people use the drug. If you take a person that ordinarily uses dissolvable tobacco products and ask them if they

1 like it, the chances are they'll endorse the product, whereas if you add to the novelty by 2 asking people who are simply smokers or moist snuff 3 4 users, they've already self-selected into using a another product. 5 So I think the key answer to that, and one 6 of the harder studies to do, would be to expose 7 people that ordinarily have not used these, and 8 then find out whether there are differences in 9 liking among naive people. I mean, that's really 10 where you're going to get the answer that has the 11 implications for uptick or use. 12 DR. SAMET: Any other questions for our 13 speaker? Patricia? 14 15 DR. NEZ HENDERSON: I'll just build upon the 16 question that was asked earlier about metabolism. We know that in African Americans, they metabolize 17 18 differently. Has there been any studies, especially in 19 this population, as it pertains to --20 21 DR. PICKWORTH: 22 DR. NEZ HENDERSON: No.

DR. PICKWORTH: Not that I know of. As I 1 say, I think the work that we're trying to do is 2 just the moist snuff, and a very small level study 3 4 is the only one I know of. My guess is, though, that people -- if you 5 look at metabolism in smokers, it's going to be the 6 same in users for oral tobacco products. 7 DR. SAMET: Okay. Thank you. 8 Moving to our next speaker, James Dillard 9 from Altria Client Services. 10 MR. DILLARD: Well, good morning, everybody. 11 My name is Jim Dillard, and I'm senior vice 12 president for regulatory affairs for Altria Client 13 Services. And we provide services for Altria 14 Group, Inc.'s tobacco operating companies. 15 I appreciate the opportunity today to share 16 some initial thoughts about our perspective on 17 18 dissolvable tobacco products, and I'm here on 19 behalf of Philip Morris USA and U.S. Smokeless Tobacco Company. 20 So as I begin, I'd like to remind both the 21 22 FDA and the TPSAC of the submission that we made in

September 2010 to the open docket on dissolvable tobacco products. We made a number of points, including that FDA should treat dissolvable tobacco products that are smokeless tobacco products just like any other smokeless tobacco products. And if such products meet the statutory definition, as outlined in the statute, of a smokeless tobacco product, then they should be treated that way.

We are committed to marketing such products responsibly to adult tobacco consumers, and importantly and correctly, dissolvable tobacco products are subject to existing legislative, regulatory, contractual and other controls on marketing and sales to youth today.

Dissolvable tobacco products present opportunity to reduce the harm from cigarette smoking. Our discussion of harm reduction in the September submission linked back to an earlier submission we made on the overall topic of harm reduction. And I appreciate what Dr. Ashley said yesterday about the upcoming session on modified risk tobacco products. We understand that

dissolvable tobacco products will be discussed within that framework, as well, but it's important for this committee to consider, within the broader context of population effects, dissolvable tobacco products in this setting.

In the December 2009 submission on harm reduction, we said that cigarette smoking is the most hazardous type of tobacco use. That harm can be reduced, on this graph, from greatest to lesser impact, number one, by not smoking, decreasing the number of years smoked, decreasing the number of cigarettes per day, and then decreasing smoke exposure per day.

We want to be clear that a harm reduction strategy must complement, not compete with, the proven strategies to discourage initiation and promote cessation. We must stay focused on these core strategies to reduce tobacco-related harm, especially for kids.

We also recognize that despite focused efforts to discourage initiation and promote cessation, many adults will continue to use tobacco

products. And for these adults, products that are proven to be lower on the continuum of risk should be made available to reduce tobacco-related morbidity and mortality. Reducing tobacco-related morbidity and mortality is a goal we share with the FDA.

We've shared on a number of occasions a representation of this approach to harm reduction. It's adapted from work done by Dr. Hatsukami and others. It shows cigarettes, on the left end of the arrow, being the most harmful, and cessation, of course, on the far right, as being the least harmful. Smokeless tobacco products are very much on the lower end of the continuum of risk and include certain dissolvable tobacco products.

Responsible product innovation can play a key role in moving adult tobacco consumers down the continuum of risk and reducing tobacco-related morbidity and mortality. That product innovation must meet evolving adult tobacco consumer interests. For example, 25 percent of adult smokers have expressed an interest in smokeless

tobacco alternatives to cigarettes. We believe that dissolvable tobacco products may be more acceptable than other smokeless tobacco products currently on the market.

For example, certain adult smokers' interest in smokeless tobacco alternatives don't want to use certain tobacco products, particularly those that involve spitting. And, as a result, we believe that dissolvable tobacco products present an opportunity to move these adult smokers who continue to use tobacco products to a lower risk product, and FDA regulation should allow for this type of product innovation.

Of course, we must do so responsibly. Such products should be subject to existing advertising and marketing restrictions on smokeless tobacco products included in the Tobacco Control Act and the Final Tobacco Rule issued by the Food and Drug Administration.

I'd like to conclude with what I believe are just a couple of key takeaways that should help guide the review of dissolvable tobacco products.

First, regulate dissolvable tobacco products that are smokeless tobacco products with existing FDA authorities. FDA should encourage product innovation in this area to take advantage of the opportunity to reduce the harm from cigarette smoking for those adult consumers who continue to use tobacco products.

I thank the committee for this opportunity and look forward to engaging on the topics in the future meetings, as well.

Thank you.

DR. SAMET: Thank you. Questions? Mark?

DR. CLANTON: No questions.

DR. SAMET: Patricia?

DR. NEZ HENDERSON: Is your company in the process of developing products like these?

MR. DILLARD: Well, I think that's a great question. One of the reasons that we're very interested in coming to this meeting is to understand what the framework is in the definition of a dissolvable tobacco product. We've certainly looked into this area, and depending on what the

1 definition of a dissolvable tobacco product is, then we may have a product on the market. 2 I'll just tell you what we do have on the 3 4 market. We have what we call a Marlboro and Skoal smokeless tobacco stick. I don't know if it's 5 dissolvable or not within the current definition. 6 It doesn't all go away. So I'm quite interested to 7 hear what the discussion is about what a 8 dissolvable is or isn't so that we can help to 9 frame that conversation, as well. 10 11 DR. SAMET: Anyone else? [No response.] 12 DR. SAMET: Okay. Good. 13 Thank you. MR. DILLARD: 14 Thank you. DR. SAMET: Our next speaker is Jonathan 15 16 Winickoff, representing the American Academy of Pediatrics. 17 18 Jonathan? 19 DR. WINICKOFF: Thank you very much. name is Dr. Jonathan Winickoff. I'm a practicing 20 pediatrician and associate professor at Harvard 21 Medical School. My research focus is on tobacco 22

control in child health care settings and child secondhand smoke exposure. I'm here today in an official capacity representing the American Academy of Pediatrics as a member and past chair of the AAP Tobacco Consortium and as a principal with the AAP Julius B. Richmond Center of Excellence.

The AAP is a nonprofit, professional organization of more than 62,000 pediatricians. We look after the health, safety, wellbeing of infants, children, adolescents, and young adults. The Academy's Richmond Center is dedicated to improving child health by eliminating children's exposure to tobacco and secondhand smoke.

The AAP welcomes this opportunity to address the Tobacco Products Scientific Advisory Committee on the issue of dissolvable tobacco products.

Pediatricians have two primary concerns related to dissolvable tobacco products. First, that children will accidentally ingest these products, resulting in serious harm or death from nicotine toxicity; and, second, that these products will be attractive to youth, facilitating and maintaining nicotine

addiction in adolescents.

In a moment, I will address each of these concerns in detail. However, I did want to say that we hope soon to share new data with the committee on the use of dissolvable and other emerging tobacco products. This data, currently under review for publication, comes from the Social Climate Survey of Tobacco Control, a nationally representative survey of public attitudes and behaviors pertaining to tobacco.

The survey is a project of the Richmond

Center and is supported by the Flight Attendant

Medical Research Institute and legacy. The results

of this survey will show that use of emerging

tobacco products is troubling high among never

smokers and former smokers.

While emerging tobacco products are often promoted as a safer alternative to cigarettes for current smokers, they may encourage those who have never smoked before and those who previously quit smoking to use these new products. When the paper is available, we will forward that to the

committee.

While we look forward to sharing the new research, we recognize that, on the whole, there is a relatively small evidence base on dissolvable tobacco. These products are a relatively new phenomenon and, as a result, do not benefit from decades of research. However, there are serious potential negative health consequences foreseeable with the expanded use and availability of dissolvable products.

Consequently, we don't have the luxury of waiting for years of data on child poisoning, adolescent addiction to accumulate before embarking on a regulatory path towards reducing these risks.

We can and must do more than merely articulate a research agenda for dissolvable tobacco. It was clearly the intent of Congress when it passed the Family Smoking Prevention and Tobacco Control Act to give the Food and Drug Administration the authority to regulate both longstanding and emerging tobacco-related threats to the public health.

The Academy is concerned about the potential for dissolvable tobacco to cause serious harm to young children through accidental ingestion.

Ingestion of tobacco products remains a major cause of unintentional poisoning in the U.S. and

70 percent of tobacco ingestions involve infants less than 1 year of age. If small children ingest unpalatable cigarettes, we can have no doubt that they will ingest dissolvable tobacco products specifically designed to taste good. The toxicity of tobacco and nicotine is well known.

In severe toxicity, one may experience skeletal-muscle paralysis, difficulty breathing, seizures, or death. Very small amounts of tobacco can be toxic to children. The estimated minimal lethal pediatric dose is 1 milligram of nicotine per kilogram of body weight.

Given the recognized toxicity of nicotine, there is a reason for great concern about potential child poisonings from dissolvable tobacco products. The serious and potential life-threatening health effects of nicotine ingestion, combined with the

easily accessible and attractive taste of dissolvable tobacco products may result in an increase in nicotine poisonings among children.

As an example, one brand of dissolvable tobacco products, R.J. Reynolds' Camel Orbs, contain approximately 1.2 milligrams of nicotine per pellet, at 12 pellets per pack, a total of 14 milligrams of nicotine in one package could be fatal if ingested by a 2-year-old child of average weight.

Camel Sticks contain 2.4 milligrams of nicotine per piece. One pack of 12 sticks contains enough nicotine to kill an average 9-year-old child. This is particularly distressing because as R.J. Reynolds said yesterday, it recently redesigned the product to deliberately make it easier to open and contained no child-proofing after the outer package has been opened.

Merely requiring dissolvable tobacco products to be sold in child-resistant packaging would be insufficient to prevent infants and children from suffering nicotine poisoning. In a

study evaluating child poisoning incidents treated in U.S. hospital emergency departments, that demonstrated that approximately 55 percent of more than 86,000 poisoning incidents in 2004 involved products that were stored in child-resistant packaging.

Unlike the bitter taste of cigarette tobacco, mint or sweetened dissolvable tobacco will be much more palatable to children and they are, therefore, more likely to ingest multiple pellets or sticks. Unlike cleaning products or other toxic household items, children are likely to view adults eating dissolvable tobacco as a food product to be consumed at will, especially due to the resemblance of tobacco products to other food products, including breath mints and candy. Young children, in particular, do not possess the developmental—mental capacity to understand the difference between a food object and a dissolvable tobacco product.

Pediatricians are also concerned that dissolvable tobacco products will be attractive to

adolescents, making them susceptible to developing a strong nicotine addiction without ever having to smoke a single cigarette. Nicotine is a highly addictive drug. An adolescent who begins to use dissolvable tobacco may quickly develop an addiction to nicotine.

Once this addiction is established, there is a risk that a dissolvable tobacco user will begin using even more dangerous tobacco products, such as cigarettes. Not only is oral tobacco dangerous in its own right, but it can add to and sustain an adolescent's addiction to smoking by permitting tobacco use when smoking is not allowed, such as at school.

Packages of dissolvable tobacco are the approximate size and shape of a cell phone, allowing children to carry them without raising suspicions of parents and teachers. They can be consumed without the telltale signs of smoke or spitting. While parents can smell cigarette smoke on their children, they cannot similarly detect the use of dissolvable tobacco products, which are

flavored like breath mints. In addition,
dissolvable tobacco products are a nearly perfect
product for a child who wants to conceal tobacco
use.

If you wanted to design a product that would appeal to youth and addict adolescents and young adults to nicotine, this would be it.

We know that adolescents' perceptions of harm differ substantially from reality.

Adolescents may believe that dissolvable tobacco products are not dangerous, especially since they resemble food products that are routinely consumed by this age group. We have also known for years that flavored tobacco products appeal to children. With this understanding, Congress banned candyflavored cigarettes, and this committee's previous recommendations support doing the same for menthol cigarettes. Dissolvable tobacco products are similarly flavored, which will undoubtedly increase their appeal to youth.

The AAP supports the use of smoking cessation therapies that are approved by the FDA as

safe and effective. All other nicotine-containing products, including dissolvable tobacco and electronic cigarettes may be harmful and must be carefully regulated if they continue to be permitted on the market.

If this committee does not come to the conclusion that dissolvable tobacco products should be prohibited, we recommend that the committee consider controls necessary to lessen their potential harm to children, adolescents, and all current non-smokers.

The Academy of Pediatrics strongly recommends the committee address the following topics. Number one, the committee should consider the public health benefits of capping the amount of nicotine in each dissolvable piece or serving, as well as in one entire package. For instance, nicotine content could be restricted to levels that would eliminate or drastically reduce the potential to cause nicotine addiction or harm through accidental ingestion.

Number two. The committee should consider

principles for reducing the likelihood that a child could ingest these products. It may be necessary to employ childproofing technology not only on the outer package, but also for each individual piece. The committee may also recommend testing regimens to measure youth accessibility of packaging.

It's important to note here that current law bars the Consumer Product Safety Commission, which typically has jurisdiction over child product safety, from regulating any tobacco product. This leaves it solely up to the FDA to ensure that children remain safe from these tobacco products.

Number three. The Tobacco Control Act
banned the use of candy flavors in cigarettes
because of their appeal to children. And in March,
this committee came to a determination that the
public would benefit by expanding this policy to
menthol cigarettes, as well. The logic behind
these actions clearly extends to dissolvable
tobacco products, as well, and, therefore, this
committee must seriously consider whether
flavorings in these products are appropriate.

Number four. The committee should also consider characteristics of dissolvable product packaging and advertising could increase their appeal to children. Packaging that uses bright colors or resembles safe products such as breath mints, for instance, may increase the risk that a young child will mistake tobacco for food.

Advertisements meant to convince consumers that dissolvable tobacco products can be consumed safely may also increase usage by children.

Lastly, this committee should consider what warnings both on packaging and advertisements are necessary to adequately convey the potential dangers of these products to children, including the likelihood of addiction. Camel's dissolvable products currently instruct users, in small print, to keep out of reach of children, but do not describe how they might be harmful. Warnings could advise against use by anyone other than current tobacco users or smokers.

Public education efforts beyond warnings may also be advisable.

Thank you very much. 1 Thank you. I was worried that 2 DR. SAMET: you were going to go even faster there at the end. 3 4 [Laughter.] DR. WINICKOFF: Just wanted to read it into 5 the record, sir. 6 7 DR. SAMET: Thank you. That was a fast read. 8 John? 9 DR. LAUTERBACH: Dr. Winickoff, how do you 10 compare the dissolvable products versus some of the 11 pictures we show of some of the NRT? And I've even 12 seen pictures of -- and I think it's called the 13 Commit mini-lozenge, which, when I looked at the 14 15 ingredient statements, did include flavors. How do you compare attractiveness to 16 children and adolescents of the NRT versus the 17 18 Camel products or the products from Star Scientific? 19 DR. WINICKOFF: Well, have you seen or had a 20 21 chance to look at some of these products, for 22 example, and smell them?

DR. SAMET: we did see some of the products yesterday.

DR. WINICKOFF: All right. Well, if you open up this package, you get a sweet, chocolate, minty, and really yummy aroma. This is highly designed to taste, I think, or to smell like a Girl Scout thin mint. When I went around my office, that's the number one thing people smelled when they read this.

So I think the product, as designed, is really to entice and addict the American people to tobacco, not to get current smokers to stop buying cigarettes, which is the reason why we have the Commit lozenge available, is to prevent people or help them to quit buying their cigarettes.

Instead, they use a safe form of nicotine, not to addict new tobacco users.

DR. SAMET: Fred, I think you were next.

DR. PAMPEL: It just seems that all the problems you mentioned about dissolvable tobacco also apply to Commit in terms of accidental ingestion and candy and addicting young people.

But the Academy, if I understand you right, is not 1 opposed to nicotine replacement therapy, but 2 they're opposed to dissolvables. 3 4 DR. WINICKOFF: Well, the Commit is designed to help people to quit smoking. It comes in bubble 5 packs, as you know. It's not loose in a container. 6 You don't open it up and a lethal dose spills out. 7 Plus, the way it's sold in a smoking cessation 8 place, in a pharmacy, signals to tobacco users 9 that, "Oh, this is something I'm doing instead of 10 smoking to try to eliminate my tobacco use, " 11 instead of to try to perpetuate it. 12 So I see a big difference between the two 13 products in how they're marketed and how they're 14 perceived by the public. 15 16 DR. SAMET: Bruce? DR. SIMONS-MORTON: You mentioned you had 17 18 survey data on initiation through dissolvables. Can you share with the committee whether you have 19 data on adolescent users? 20 DR. WINICKOFF: We don't have adolescent 21 22 users in that survey; we have 18 and over. And I'd

like the material to go through peer review before it's considered by the committee. But as soon as it does, you can be sure that you'll have it.

One of the concerns and one of the things we addressed in the survey was looking at a range of different novel tobacco products, not just dissolvables. And we feel that as the number of tobacco products expands, the potential to become an initiator of tobacco use similarly expands. This is because there can be niche marketing to different groups. And so that's one of the things that we looked at in the survey, is a range of different products, dissolvables being one of them.

DR. SAMET: Is the survey a national survey?

DR. WINICKOFF: It is.

DR. SAMET: Okay. Thank you.

I think, Dan, you're next.

DR. HECK: I thank you for your comment, Doctor. We heard some presentations yesterday about some of the poison control center data on pediatric intoxication from tobacco products.

Can you give me a sense -- we heard you

mention potentially fatal intoxications. Can you 1 give me a sense of how many fatal intoxications 2 there are from tobacco products, generally, or with 3 4 specific subtypes of products? I know that a cigarette has roughly 10 milligrams of nicotine in 5 it, and these products seem to have 1 or 2. 6 What are the data on fatal intoxications? 7 DR. WINICKOFF: I don't know how many fatal 8 intoxications there are. I think it's difficult 9 for any age child to eat enough cigarettes, because 10 11 it's an unpleasant experience. I've had the personal experience of my 2-year-old eating a 12 cigarette butt, and eventually she did just cough 13 it out and spit it out. I'm worried that if she 14 sucked on something sweet, it would probably be 15 16 swallowed. So I think there's a quantitative and 17 18 probably serious difference between putting 19 something that's sweet in your mouth and something as unpalatable as a cigarette in your mouth. 20 21 DR. SAMET: Patricia? 22 DR. NEZ HENDERSON: Are there any

recommendations for screenings, like when adolescents are screened at a clinical setting to ask about tobacco products? I know general questions, do you use any form of tobacco products.

Is your organization thinking about expanding that? Because a lot of youth probably don't think that these dissolvables are tobacco products.

DR. WINICKOFF: This would likely just drop off of the -- honestly, this would likely drop off of the list of things that pediatricians have to get through in 10 minutes with a teen.

I think that we can ask about cigarettes.

We can say tobacco. But once you start expanding
to "and any tobacco-containing sticks, any tobaccocontaining Orbs or dissolvables or strips or
hookah" or any of the other forms, newer forms of
tobacco that are out there, it starts to be a very
difficult task to screen. And that's why limiting
the number of products is probably wise from the
standpoint of limiting teenage exposure to tobacco
products.

DR. SAMET: Do you know, or does anyone know -- maybe FDA knows -- in terms of the ability of children to access these products, are there any sort of standard tests where you put things, containers in front of children and allow them to have at it?

DR. WINICKOFF: There's an interesting balance here. The harder you make a package to open -- and it may be the kind of thing that we just can't prevent these types of intoxications. The harder you make a package to open, the more impossible it is, the more likely a grownup will just leave it open, in your purse, on the table, because, boy, is that hard to open. So you leave it open, and then kids have access to it. Make it too easy and you know those smart kids will figure it out.

So it may be the kind of thing where there's a curve. You're figuring out -- you're balancing two things, and there's a science probably to that that needs to be studied.

DR. SAMET: That was actually my question.

Is there a science or any form of --1 DR. WINICKOFF: I think it would be 2 appropriate, yes, to move in that direction. 3 4 DR. SAMET: David, do you know? DR. ASHLEY: No. 5 DR. WINICKOFF: I'm not sure. 6 DR. SAMET: Okay. Thank you. 7 Other questions? Mark? 8 DR. CLANTON: Yes, I do have a question. 9 Obviously, Dr. Winickoff, this is our first meeting 10 on dissolvables, and already we have two areas of 11 inquiry that have formed in terms of things we need 12 to know more about. One, obviously, is potential 13 for pediatric poisonings, and the other is the 14 potential for nicotine products to affect health, 15 16 other than cancer or lung disease-related issues. You mentioned in your presentation that 17 18 there might be other health effects, either on adolescents or children, that might come about as a 19 result of, I guess, continuous or prolonged use of 20 this kind of product. 21 22 Are you able to describe any of those other

health effects?

DR. WINICKOFF: Well, going back to 1953, we've known that the dermal application of tobacco toxins has caused cancer. That first study was by Wynder in 1953, where he painted tobacco toxins on the bodies of naked mice, and all of those in that intervention group did end up getting cancer, whereas none of the control mice who were painted with acetone got skin cancer.

Now, there is data on orally-ingested tobacco, mouth cancer, esophageal cancer. So this is not a big stretch that when you bathe the GI tract in carcinogen, you will develop some amount of cancer, and that's why we can't say that these products are safe.

In addition, there's a enterohepatic circulation when you ingest tobacco toxins which occurs. So, for example, is there a potential for long-term liver damage that you might not suffer if you smoked a cigarette? I don't think that that is well studied. However, I'm not an expert in the adult diseases, where typically this stuff might

show up 20 or 30 years later.

DR. SAMET: Dan?

DR. HECK: Just a little follow-up, a comment more than a question. I guess, in the interim, I did look up, from the poison control center, the most recent year of data, and the number of fatalities from tobacco products-pediatric is zero for the most recent year.

I also mentioned yesterday -- I guess you had missed -- there is a paper coming up at the clinical tox meeting in September that reports on a number of instances, cases of pediatric ingestion of dissolvable products. And that author is concluding that serious toxic outcomes are unlikely for that class of product.

DR. WINICKOFF: Well, I really respect that research. I'm familiar with it, as well. We have such a thin picture here of what the potential dissolvable market could be.

Now, when you have a container like this -- now, remember, the dissolvables up to this point had mostly been in the bubble packs, very

hard for a child to get into the bubble packs. But if you look at these strips; here they are.

Basically, you get into it and the entire dose falls out of the package. So what you have here is the entire dose available to a child to ingest as opposed to -- imagine a child really eating a package of cigarettes; not very likely.

So I think that that data we need to approach cautiously and not say that's a green light for us to say that, oh, yeah, we don't need appropriate packaging to protect children from ingestion.

DR. SAMET: John?

DR. LAUTERBACH: Yes, Dr. Samet. I just want to correct one thing. Unless my tobacco science is awfully bad, I believe Dr. Wynder's skin painting studies were done on smoke condensate.

The second thing is there are a couple papers out in the literature already -- one of them I've given to the TPSAC DFO for circulation -- in which we've looked at measures, in vitro measures of toxicity of some of the more hazardous smokeless

tobacco products, such as moist snuff. And, 1 basically, you're hard-pressed to find any sort of 2 response in either the Ames assay or in the in 3 4 vitro micronucleus assay. DR. WINICKOFF: And the Ames test -- test in 5 a Petri dish, basically. 6 DR. LAUTERBACH: Yes. 7 DR. WINICKOFF: But it would be nice -- I 8 mean, we don't know the experience in humans yet. 9 DR. SAMET: Okay. Patricia? 10 11 DR. NEZ HENDERSON: Accessibility to youth of these products is probably just like cigarettes, 12 13 right? They can get access to it. So I'm just concerned about, I guess -- these look very 14 appealing, and I said this yesterday. I'm like, 15 16 I've never smoked in my life, but the fact they're out there in these forms makes it easy to ingest. 17 18 So I'm wondering, has there been any discussion with the Academy about what you are 19 doing with these products, whether they're putting 20 it into alcohol and having it dissolve like that, 21 22 or maybe put it in marijuana sticks? I have no

idea. 1 If you can imagine it, you 2 DR. WINICKOFF: can bet that teens are going to try it. 3 4 [Laughter.] DR. WINICKOFF: But I don't know the data on 5 what teens are actually doing now. Again, a very 6 limited amount of data out there right now. 7 DR. SAMET: Neal? 8 DR. BENOWITZ: Jonathan, there was a 9 submission in our docket from a research group in 10 11 Virginia which surveyed adolescent perceptions based on the packaging and concluded that, I think, 12 27 percent adolescents said that they would really 13 be interested in trying this product based on the 14 packaging. 15 16 Is your social survey planning to look at this question of how attractive this is potentially 17 18 to non-smokers, to the kids who are not smokers? 19 DR. WINICKOFF: That's a really insightful comment. I think what would be particularly 20 enlightening is to look at whether people would be 21

planning to try this product versus planning to try

22

cigarettes, seeing where the overlap was, so that 1 then you can use sort of intention to experiment as 2 a guess as to what people will actually do. 3 4 theory of planned behavior, we think that intention would predict behavior. So I think we'll try and 5 add some questions on that. 6 Thanks. DR. SAMET: Bob? 7 DR. BALSTER: Does the Academy have a 8 position on whether or not these products should be 9 labeled with respect to their nicotine and/or 10 toxicant content? 11 DR. WINICKOFF: Not a formal position. 12 However, we favor the increased disclosure of and 13 more complete warnings so that people can 14 adequately assess their risk. 15 16 DR. SAMET: John? DR. LAUTERBACH: Dr. Samet, could we have, 17 18 for the next meeting, or have the FDA get and send 19 out a picture of this ad that was used, or this test vehicle that was used in this Virginia study? 20 21 DR. BALSTER: The report on that, actually, 22 is on the comments that were submitted. So there's

a full report with sort of the pictures. 1 don't quite have the method in there, but it's 2 online. You can get it. 3 4 DR. SAMET: I will say there's a lot of material on the public docket that is -- you have 5 to go through everything to find what is there, 6 unfortunately. It's not particularly well indexed. 7 But if you open up the folder of the public docket, 8 the methods are there. 9 Any other questions for our speaker? 10 11 [No response.] 12 DR. SAMET: Okay. Thank you. 13 DR. WINICKOFF: Thank you. DR. SAMET: We'll move on next to Greg 14 Connolly, Harvard School of Public Health. 15 16 Greg, I guess forever a former member of TPSAC. DR. CONNOLLY: Thank you very much. 17 My name is Gregory Connolly. I'm a Professor of Public 18 Health at the Harvard School of Public Health. 19 Му travel is being paid for today by the American 20 Legacy Foundation. I have no other conflicts of 21 22 interest.

I just want to make the observation,
listening this morning, it was really intriguing,
and the first speaker I think reinforced my
perception, is that I really believe FDA and the
tobacco industry should leave this room, enter into
a consent agreement to lower the levels of nicotine
in combustible cigarettes to that of tomatoes
before the next meeting and do it by the year 2020,
and then come back to this committee. And we can
avoid ourselves a lot of wasted time over the next
10 to 15 years, and we can address the dissolvable
products.

As long as they have a combustible product in the marketplace competing with a dissolvable product, we're having chaos. This was 1917. We had one product. Today, we have from R.J.

Reynolds, Camel, a total grand experience. We've got multiple products. We've left the century of -- the cigarette century. We've moved into the century of multiple product use, where one product would actually enhance, maintain, initiate; the other product would be a substitute, offer dosing

sometimes at a very low dose that rewards the dopamine reward system. So when a person leaves a bar, the first thing they do is they grab a Camel cigarette, because they've had a low dose of nicotine. It acts as a primer on the dopaminic reward system.

We did some research when the Orbs first came out. This is when it first came out. It just caught my eye, saying this is really insane. Who would want to do this? Who would ever in their right mind want to take a drug like nicotine and make it appear like a product that's highly appealing to children?

So we did some research on, if I can show.

I think one thing that was surprising was the Orb

had a fairly high pH, 8, which is higher than we

find in snuff. So the actual absorption is

42 percent on ionized nicotine. So your free

nicotine content of the Orb is actually higher than
that of moist snuff, 28 percent.

I am concerned with ingestion, but, also, since these are dissolvable in the mouth, if a

child lets it reside in the mount, based on data presented yesterday from the VAT study, the absorption could be far, far greater than we'd see in the GI tract, contributing to much higher problems. And this was just at the beginning of the study.

I don't want to redo what Jonathan spent, but in our estimations, we've tested Orbs, we found 1 milligram per pellet, 10 to 15 pellets. We reached the lethal dose, as determined by science, sticks 3 to 5, and then strips 12 to 4, and this is based on the body weight of a 1-year-old.

We analyzed the data and we came up with a number of tobacco poisonings over a three-year period, reports to the poison center. And I think of these, there was one death. But that's one too many, in my opinion. To have a child die and say, well, that's not a big deal I think is a very cruel, cruel thing to say, in my opinion.

Then R.J. Reynolds, when confronted with this data, they come back -- which I found really comical. We only had 6,724 -- we only, only. If

any other drug manufacturer or food manufacturer came before an FDA committee and said we only had 6,700 reports, they would be asked probably to leave the room and come back to the committee with data.

Then RJR comes on to say in their report that we're not aware of any dissolvable product.

Well, there was one in a test market. We are prevented by IRB from reporting who that individual was. Furthermore, we have not received any postmarket reports. And that, to me, is very curious.

RJR is here, and I would just want to ask

RJR, how many reports have you had from death of

Camel lung cancer cases reported to you in the past

year?

Could you stand up, please, and report to that, to the committee? How many people died from smoking Camel cigarettes from lung cancer? You didn't pick that up in your reporting system, I imagine.

Well, after our report came up, RJR had withdrawn Orbs because of poor sales, supposedly,

because they were being dispensed one at a time. So as Jonathan just adequately showed, now, when they're confronted with science, that there is a potential problem here, they make it even easier. And why so? Well, because our federal government, our court system made a finding. And it stated the government has proven that the enterprise -- and that is the tobacco industry defendants -- not all of the tobacco industry companies here were defendants on this case, so I will qualify that, saying the defendants knowingly and intentionally engaged in a scheme to defraud smokers and potential smokers for the purposes of financial gain by making false and fraudulent statements, representations and promises.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

This is not your average drug company we're listening to, or your average food company, and the FDA has an obligation to consider what another arm of the federal government has found when considering evidence presented by the tobacco industry.

I asked the question, if we can put

dissolvables in a package to protect kids, why can't we put Camel cigarettes in a package to protect kids? Why can't TPSAC and the FDA recommend that cigarettes be only sold in childproof packaging if it's illegal to sell to children?

I would also point out that as was questioned, the concern is with ingestion with infants. But keep in mind, these products are being promoted to pregnant women, potentially, exposing a fetus, breastfeeding women, individuals with cardiovascular disease. And the Swedish study on snus raises serious questions about cardiovascular risk; people who are long-term smokers, who have probably had an enormous amount of cellular damage done to the lung tissue, who then are just continued exposed to TSNAs. And we don't know whether sequelae will be that for the person, and, also, continued use.

I think to understand this, you have to look at combined use, though. You have to look at oral tobacco. Unfortunately, we don't have a history of

that.

RJR clearly state we designed Camel dissolvable products to complement its current tobacco products. It didn't say this was a substitute. Philip Morris calls it an adjacency product. Neither company has said it's a substitute.

Again, I urge the tobacco companies today to go meet with the FDA tomorrow, enter a consent agreement, and lower the level of nicotine in your cigarettes by the year 2020 to that of tomatoes, and we can all go home and stop wasting our time. And then we could explore these issues in a rational manner.

Sweden, we have not seen a reduction in current smoking, current defined by one cigarette during the past month. Among adolescents in Sweden who use snuff, 71 percent smoke cigarettes, 20 percent of males also are current smokers.

A study just came out June 3rd from Sweden, the largest prospective study on the use of tobacco products to date, states the increase in snus does

not seem to -- the smoking prevalence does not seem to be influenced by snus, the largest prospective study to date showing in Sweden that snus has not had an effect on smoking prevalence decline in Sweden.

If we turn to Norway, among males, in '85, it was 9 percent among occasional snuff use. Now it's 33 percent; absolutely no change in daily smoking. Of course, Norwegians will never think they're, in any way, shape or form, related to Swedes, but I tend to believe they are of the same stock.

This is frightening data. This is data from YTS looking at current high school students by sex who use smokeless tobacco. We were making great progress from '95 to 2003, until RJR took over Conwood. And, oh, by the way, RJR, why do you only lower your TSNAs in snus? Why don't you do it in the Conwood product? Does Conwood uses somehow less of Americans? They deserve less protection? We only lower the levels of nitrosamines in snus or in Orbs. We won't touch the Conwood product. Does

that cost you too much money to make that safer, 1 RJR? 2 Does it? 3 4 [No response.] DR. CONNOLLY: This stat is disturbing. 5 We're seeing a sharp increase of male use. I just 6 left a conference in Texas where America was 7 present, on smokeless tobacco, and I heard from 8 people from Oklahoma, from Arizona, from the 9 southeast, from Indian reservations about the surge 10 11 in smokeless tobacco use among young people, because, in part, we're educating and telling young 12 people it's okay to use these products; these 13 products are fine. 14 15 Then when we go on and we further break down 16 the data. Among our 18 through 25-year-old cohort, 66 percent are also smoking if they are current 17 18 smokeless tobacco users. Enormous levels of dual 19 use. We're entering a century of dual use, where 20 products with very low nicotine levels can be 21 22 served as primers to the dopaminic reward system,

and for every high levels, they could become 1 substitutes. 2 I would point out, to Neal's question, we 3 4 look at one product, but if you go on Facebook, there are 600 sites solely dedicated to Skoal. 5 The Camel Snus website says, "Well, to get a buzz, take 6 four. " And what protects a child from taking four, 7 eight, nine to get the same buzz from cigarettes? 8 Easily done. 9 Greg, you need to wind up. 10 DR. SAMET: 11 DR. CONNOLLY: Okay. Cancer risk estimates, go with your technique. It's only a practical 12 standard. It is not a health standard. If you 13 apply EPA standards, the magnitude of risk is 14 twofold, 2,000 times greater. 15 16 If you are a committee of scientists, you will abide by the FDA's levels on nitrosamines. 17 18 You will not embrace a performance standard. 19 Thank you. I'll be happy to answer any questions. 20 21 DR. SAMET: Okay. 22 DR. CONNOLLY: One stat, just one.

metals were not tested. These are heavy metals in 1 Orbs, strips and mints. 2 They grossly exceed -- that should be 1 nanogram per gram. 3 4 DR. SAMET: Okay. I think we'll move on. We'll move on to questions. 5 DR. CONNOLLY: We're done. Fine. 6 Thanks. DR. SAMET: 7 Thank you. Are there questions or comments for Greg? 8 Patricia? 9 DR. NEZ HENDERSON: Dr. Connolly, it's 10 11 always great to see you and hear your presentation. Are there dissolvables in other countries? 12 DR. CONNOLLY: Taiwan, Brazil have been 13 introduced. R.J. Reynolds just introduced 14 dissolvables in Taiwan, I think Brazil. Dr. Evans 15 16 spoke to that. I got a report from South Africa this morning where, to one question, e-cigarettes 17 18 were found to have Viagra in South Africa. they're going to be scheduled by the South African 19 government for medicinal use only, which I thought 20 21 was very funny. 22 Yes, there are. And I think we're seeing

the same phenomena globally, where Philip Morris
International is merging with Swedish Match to
develop an international market. VAT is going
international with smokeless tobacco.

The whole problem is moving to a multitobacco market. The purpose of this law was to
draw a line in the sand and say no new products.
Well, let's fix the problem as it is. As the
committee knows, FDA has received, for substantial
equivalency, 2,584 requests. And as the committee
knows, the FDA has received zero requests as of
April 1st of this year for new products.

I just go back to that court finding. Zero requests from our friends from the tobacco industry for new products since 2007. Everything is substantially equivalent.

DR. SAMET: Okay. Other questions? Mark?

DR. SAMET: Greg, I just wanted to be certain. The data you showed, the use data, I was trying to understand that there's information in these datasets about both smokeless generally and

DR. CLANTON: No questions.

cigarette use, the dataset you were pointing to.

DR. CONNOLLY: I obtained that from CDC.

CDC, hopefully, will cooperate with the FDA and make sure their data is available. But it's showing a large surge in combined use among current users. If you have used during the past 30 days, smokeless tobacco, and 66 percent of the cohort, 18 through 25, males, have also used smokeless tobacco products.

So combined use. And CDC is very concerned, for two reasons. It is not the dose of cigarettes that contributes to disease. If you quit smoking at 35, your risk, according to Peto, is going to fall of pretty heavily to multiple diseases. It's the length of exposure.

So to the extent that smokeless tobacco products even can lower the number of cigarettes smoked per day, but have a person continue to smoke from 35 to 40 to 50, 55, disease risk is going to increase greatly to population level, according to the Federal Centers for Disease Control.

So when we look at that data, we're looking

at a very, very big warning sign to our nation that 1 we have to be very cautious about combined use of 2 these products. 3 4 DR. SAMET: Patricia? DR. NEZ HENDERSON: Greg, can you go back to 5 the previous slide? 6 DR. CONNOLLY: I'll try. Could someone? 7 DR. SAMET: Hang on one moment. 8 This is on calculated cancer 9 DR. CONNOLLY: This slide here -- Gothia is a performance 10 risk. 11 standard. It's like you set performance for It is not based on science. FDA has set a 12 brakes. standard of 5 nanograms per ml for TSNAs in bacon 13 and baby bottle nipples. Gothia technique talks 14 about 10,000. 15 16 Now, if this committee wants to undo what other FDA committees have done on standards of 17 18 TSNAs, then go ahead and do it. But forewarn the 19 other 43 FDA advisory committees that you're setting your own standard on TSNAs in a product. 20 21 Heavy metals, the concentrations, again, are 22 far greater than allowable. Now, I'll just go to

the heavy metals. There was no discussion of heavy metals yesterday. These products, the metals are hard to get out. That's one of the issues. It should be 1 nanogram per ml, not 1 milligram. I'll correct that.

But the heavy metal concentration is high, and we know heavy metals contribute to disease. That should be looked at very, very carefully. And as a scientific committee, you are not here working for the Auto Safety Commission. You are working for the Federal Food and Drug Administration, and you have to stick with the science. And if there is scientific body out there that has established levels for TSNAs, then you don't have to look to a tobacco company in Sweden to tell the United States Food and Drug Administration what is safe and what is not safe.

DR. SAMET: Okay. I think you've answered the question. Let's see.

John?

DR. LAUTERBACH: Just a question on one of Dr. Connolly's comments concerning levels of

nitrosamines in bacon and baby bottles. 1 Dr. Connolly, I think you VNAs, not TSNAs. 2 DR. CONNOLLY: VNAs, yes. But, John, one 3 4 could easily go in and look at the literature and establish an equivalent level. 5 DR. SAMET: Dan? 6 DR. HECK: Actually, that was my question, 7 the source of that cancer risk, that potency value. 8 And, also, on the heavy metals slide -- I caught 9 briefly, you said there's a typo or something 10 there -- what is that EPA value there, that 11 reference value? What is that? 12 DR. CONNOLLY: It's ambient -- I'm sorry. 13 It's ambient air level value. But this committee 14 could get ingestion exposure levels for heavy 15 16 metals very, very easily from various sources --DR. HECK: I think that would be more 17 18 appropriate. 19 DR. CONNOLLY: -- and then place it against what we see in the Orbs and come up with a 20 21 scientific standard. So we are not playing with performance standards. It's a very dangerous area 22

1 for a health group to be playing with performance standards for an industry that's been found in 2 court to be acting in a manner that's not in 3 4 keeping with the spirit of America. DR. HECK: I do think another value other 5 than an air standard would be much more appropriate 6 in such calculations. 7 DR. CONNOLLY: We'll supply that to the 8 committee. Be happy to do that. 9 DR. SAMET: Okay. Thank you for your 10 11 comments, Greg. DR. CONNOLLY: Caveat emptor. 12 Committee Discussion of Questions to the 13 Committee and Next Steps 14 DR. SAMET: The open public hearing portion 15 of this meeting is now concluded and we will no 16 longer take comments from the audience. 17 18 committee will now turn its attention to address the task at hand, the careful consideration of the 19 data before the committee, as well as the public 20 21 comments. 22 So, first, let me see if there are

additional reflections that the committee would like to offer on the public comments that we have just heard, and then I think we should turn back to the questions that we began with from Sarah on that first slide of issues. And then I would like us, I think, to do some consideration of additional materials that we may want to see.

Actually, as a reminder, Greg's slides had the IARC Monograph 89 listed, which was published in 2007, probably covers the literature through about 2005 and would be another useful resource for us to look at as a comprehensive review on at least the smokeless tobacco data through that particular point.

Neal?

DR. BENOWITZ: I had one comment based on the Altria presentation, which argued that dissolvables and smokeless tobacco should be considered together. This also brings up some of the other questions about product specifications.

It seems to me if we're evaluating the health risks, we really need to consider the

differences in the products. And this committee, if we look at smokeless tobacco broadly, as Altria says, then the health considerations are totally different than if we look at products that are specified to be really low in nicotine and nitrosamines.

So I think the committee needs to really address the question of what we want to consider.

And if we're talking about dissolvable products, what doses of nicotine and toxins are we including?

I think that's a major question about what are we really talking about.

DR. SAMET: So is your suggestion, in part, that we need a committee working definition or categorization of the different types of products?

DR. BENOWITZ: Yes. And I think we need to focus in on -- if we give a report on dissolvable products, we need to say exactly what is being included there, including product specifications based on what's currently available now, and whatever conclusions we come up with may not apply to products that fall outside the specifications.

Again, it gets to the question about how 1 generalizable can we be about dissolvable products 2 3 as a name. 4 DR. SAMET: We've heard from FDA already that the Act does not specifically define 5 dissolvables, if I have that correct. 6 Let me ask. Internally, have you, in your 7 mind, come to some sort of working definition or 8 9 categorization? DR. ASHLEY: You can ask the question. 10 DR. SAMET: 11 I did. 12 [Laughter.] In actuality, no, we haven't. 13 DR. ASHLEY: We, again, have a general sense of what we thought 14 of, the specific products we thought of, that led 15 16 us to invite particular companies to come and present. But we have actually not developed our 17 18 own definition of dissolvable. We are very 19 interested in what the committee might develop, and that is a means of refining our very broad concept. 20 21 DR. SAMET: Bob? 22 DR. BALSTER: I haven't formed an opinion

think, at the very least, we ought to get a similar quantity of information on some of the nearby products that could be potentially -- some of the other smokeless tobacco products, for example, like snus, to get a full retina of information on them, even if we ultimately decide not to include them in the dissolvable group, because I don't think I'm able to figure out where to draw that line without really seeing some of the boundaries. And, of course, I suppose the same thing could be said for NRTs, but I'm thinking more on the other direction.

So I would encourage us to seek from the sponsors and/or other sources information on other smokeless tobacco products that could border on the dissolvables, with the idea that would help inform us where we think some lines could be drawn.

DR. SAMET: So I think just to state the obvious, it will be hard for us to write a report on dissolvables without saying what we're writing a report on.

DR. BALSTER: I think we ultimately do have

to, obviously, decide it. But I'm saying without seeing the full plate, how do we make the subdivision?

DR. SAMET: Dan?

DR. HECK: I think we're all wrestling with the same issue that Jim Dillard presented, where the -- I've never seen the product, but I've seen pictures of it, their novel product. It's a stick of some sort with a snus applied to the end, where you get an element of hand manipulation and the use of the product. It's kind of a hybrid, I guess. It's not quite traditional smokeless and not quite dissolvable either, and we may well see other such products that don't quite fit our traditional definitions, even recent definitions of dissolvables.

So there's an advantage, certainly, of thinking more globally, trying to capture all of these products, as well as the narrow directive from FDA to try to nail down the products that essentially, I guess, go away in use and don't have a packet or a cigarette butt or a stick, I guess,

after use. 1 DR. SAMET: So I think we should keep this 2 on our list of things that we have to deal with. 3 4 Other comments after the public hearing? John? 5 DR. LAUTERBACH: Dr. Samet, we had the 6 question of heavy metals come up. I know there are 7 some studies out there, and I could probably get 8 these to you afterwards, where people have looked 9 at conventional smokeless tobacco products, 10 essentially, how many of the heavy metals are 11 actually bioavailable, and I think we need to have 12 that. 13 I think even if you look at your normal 14 vegetables, there are a lot of these heavy metals 15 16 there, but because they're entrapped in proteins, we don't have a biohazard in terms of human 17 18 consumption of our normal fresh vegetables. 19 DR. SAMET: And, of course, there are a variety of metals in tobacco smoke, as well, so it 20 would be good to have that. 21 22 Patricia?

DR. NEZ HENDERSON: Just in terms of, I 1 guess, the charge that Congress has charged us, can 2 you put that up there just so that I can better 3 4 understand? This is the original --5 DR. SAMET: DR. NEZ HENDERSON: The original, yes. 6 DR. SAMET: -- the charge, going back to 7 yesterday's presentation, the public health impact 8 charge. 9 DR. NEZ HENDERSON: Right. 10 11 DR. SAMET: Which is quite similar in style to the menthol charge, in fact. 12 DR. NEZ HENDERSON: Because I'm just -- I 13 guess the question that I have is just in terms of 14 our role -- I guess our role in making a 15 16 recommendation, I'm just a little bit confused. guess there's a lot of uncertainty with what we're 17 18 supposed to be doing. Well, again, I think the analogy 19 DR. SAMET: to where we were when we began menthol is entirely 20 21 appropriate, and I think there we -- again, what 22 was critical was thinking about how to frame the

evidence in a way that would address that broader charge, the public health impact charge.

Again, I think, as I alluded to when I sort of -- at least mentally reviewed the menthol framework, said that it would be, in fact, probably different as we approach these products. So I think we'll have to think about how different it may be.

I mean, we're left -- if you look at this, we do have some of the exact same issues, the so-called public health impact, risks and benefits in the first, and then, again, the likelihood that people will use such products, and then the possibility that those who do not use tobacco products will start using. So it's the initiation question.

I think some of the same general questions are here. I think what we lack is a historical record, and we lack information about various aspects of these specific points for dissolvables, per se, by the fact they're just newly on the marketplace and there were 22 articles.

Neal? 1 DR. BENOWITZ: Besides the charge to assess 2 the impact on public health, can we also include 3 4 recommendations on how to reduce the impact? example, if we say that there should be individual 5 blister packaging, is that within the realm of what 6 we can recommend? 7 DR. SAMET: I think we're allowed to make 8 whatever recommendations we want to make. 9 these are recommendations to FDA, and I think, 10 11 presumably, we can be as general or as specific as we want to be. 12 John? 13 14 DR. LAUTERBACH: Are we to the point, Dr. Samet, where you're looking for information we 15 16 could use as this committee? DR. SAMET: Just any comments at this point, 17 18 and then I think I want to go back to these slides 19 and get us a little organized. But, please, go ahead. 20 DR. LAUTERBACH: I would like to see the FDA 21 22 get us the standards for F-1 and F-2 packaging.

Someone should know what that is, maybe out of 1 CPSC, but there are definitions. 2 Anything else? Mark, do you 3 DR. SAMET: 4 have anything you want to weigh in with? DR. CLANTON: Nothing to add at this point. 5 DR. SAMET: So if we could go back then to, 6 I think, Sarah's slides. 7 MS. COHEN: The questions? 8 9 DR. SAMET: The questions, yes. So these were some of the general 10 Okay. questions. And I think what would be useful is to 11 think about what additional information might be 12 available or what other sources we would like to 13 have. Again, this relates to our future meetings 14 15 and information-gathering. 16 Marketing, we've heard from the two companies that have products on the market now. 17 18 Are there other things about marketing that we'd 19 like to know about, or perhaps consultants that we would want to bring in, in this area? 20 21 Neal? 22 DR. BENOWITZ: I'd like to know what the FDA regulations say about marketing right now. What kind of limitations occur? I don't even know what the guidelines are for what manufacturers can and cannot say about their products.

DR. SAMET: David?

DR. ASHLEY: I don't think I can respond to that right off the bat because I'm not familiar with that piece right off the bat. But we can see what the statute says specifically.

DR. SAMET: Patricia?

DR. NEZ HENDERSON: It would be nice to see the different types of marketing that these companies are using right now in magazines, store ads, wherever. So someone that just can give us a good picture of what those ads look like.

DR. SAMET: Do we want to know anything about -- again, where there's more experience, do we want to know anything more about not only dissolvables, but smokeless, in general?

I'm not sure who would be the right person or people to tell us about that and whether we want to hear from the companies on that, or we want to

have a marketing expert talk to us.

Bob?

DR. BALSTER: I guess, in my mind, I had envisioned that a letter, unlike the ones that the FDA sent to Star and RJR asking for specific information about these topics, a similar letter go to the manufacturers of other ST products that we think are kind of relevant here, which, certainly, I think might include snus, and solicit that information from the companies in the same manner in which that information has been solicited for the ones that we have.

I don't know if that's a problem to write the same letter, basically, to a broader array of companies, asking about a broader array of products to get, in effect, comparable information about them as what we are being given about these so-called dissolvable products.

DR. SAMET: I guess the question, for example, with snus -- and, again, this goes back to what other types of smokeless products might be useful for our task. So with snus introduced into

the marketplace relative recently, but with several more years of experience, would this be useful for us? I see some heads suggesting yes.

DR. BALSTER: I don't know if it's possible to get more information on the Swedish experience, if that's something we can request or not. I don't know what the story is there, but that seems like probably the most experience on that.

We've seen information, a lot of it, and it's being used in some of the modeling and various other things. I mean, I think we have to have a full understanding of that Swedish snus experience. And I don't know from whom to get it, whether there would be independent experts that could come and give it to us or whether we would ask --

DR. SAMET: Let me ask David if we could ask

FDA to provide an overview of the Swedish

experience. I mean, there's a fairly substantial

published literature on this.

DR. ASHLEY: My biggest request is that the committee -- if the committee wants to address dissolvable tobacco products in a realistic

timeframe, that we make sure that you are focusing your questions as much as possible. If we, for example, ask about all the marketing of smokeless tobacco, realize that that's going to mean a huge amount of work. I'm afraid it may make menthol look like a very easy walk in the park.

So my request is that the committee, make sure you focus on the questions that will help you to understand more about dissolvables. And be careful what you ask for. Again, I'm not going to try to limit what the committee wants to discuss, but be aware of the volume of information that you might encounter, depending on exactly how you're asking those questions.

DR. SAMET: Okay. So let me go back to my question to you, which was, specifically, if we wanted to get a closer look at the Swedish snus experience, would it be appropriate to ask FDA staff to bring together the papers around that story that are in the peer-reviewed literature, as you have summarized other bodies of literature for us?

Your comment was a more general one that I'll come back to, but my initial question to you was on the snus issue.

DR. ASHLEY: I think it's very possible for us to pull together the papers related to snus. As you said, there are many, many of those. There are definitely different viewpoints on the interpretation of that data, and we can make an attempt to try to pull those multiple viewpoints together, if you think that that Swedish experience around snus will be helpful for the committee in looking at dissolvables.

DR. SAMET: And I think the issue -- and this goes back to some of our conversation yesterday about, in fact, what lessons learned from other smokeless products may be of value to dissolvables. And, of course, this is a matter of conjecture, in part, but I think we're going to have to seize on some things that we think may be useful.

I think the thought on the marketing would perhaps -- would certainly not be all smokeless

products. I mean, I agree that that opens the door to far more than we want to see. The question, I think, was whether, again, for example, the marketing of snus as a new product on the market, coming sort of within the same era of restrictions on smoking, would be valuable because we could see how it was marketed and try and understand the marketing in relationship to the use patterns, again, with the anticipation that this might be something we would then generalize to dissolvables, I think, to phrase how this would play out.

Neal?

DR. BENOWITZ: I want to support that. We heard from Dr. Curtin this elaborate model based on Swedish initiation data. We cannot use such data without having a really good understanding of the marketing and the culture.

So if we're going to consider such data, we have to have the context and compare it to the U.S. context. We cannot take it in isolation.

DR. SAMET: Dan?

DR. HECK: The topic may have passed in the

conversation here, but we might think about, in defining our turf here on dissolvables, the concept of a practical definition of these products as an oral -- I guess oronasal is in the statute, but I'm unaware of any products like that.

An orally consumed tobacco product, in the normal consumption, the product unit is totally absorbed or dissipated. There's nothing left over, in a sense. And I think reference to the snus literature, as we heard yesterday, given the similarity of the tobaccos in these types of products -- these tobaccos are cured in a manner that minimizes the formation of these tobaccos specific nitrosamine carcinogens. There is no fire-cured tobacco, as in some traditional moist snuffs, that carries with it some introduction of benzo(a)pyrene.

So there is a lot of similarity in the tobacco composition. So there is a natural extension, I think, that could reasonably make reference to the snus literature to move us ahead with maybe a practical definition that these

products just go away during their consumption as 1 opposed to being expectorated or a butt put out. 2 Okay. I'm keeping sort of a 3 DR. SAMET: 4 running list of things that I think that I'm hearing or additional information we may want to 5 have. 6 Let's move down from A to B here. 7 Perception, use of dissolvable products by children 8 and adults. And, again, it sounds like some data 9 will be forthcoming here. 10 Patricia? 11 DR. NEZ HENDERSON: I'm just looking at this 12 ad that Star has at the bottom. 13 It says "Say goodbye to boundaries." And how this impacts 14 15 tobacco policies throughout the country and many 16 communities, they are going tobacco-free. hear the experience, I guess, from those 17 18 communities that have gone tobacco-free. 19 Is the tobacco industry just trying to --DR. SAMET: You mean smoke-free. 20 DR. NEZ HENDERSON: -- circumvent these 21 policies? I guess I'm just kind of thinking about 22

Nation, we had proposed to go commercial tobaccofree in hope that people would quit smoking or quit tobacco use. Well, we haven't gone there yet, but with other communities, they have gone that route. So to hear from their experience whether cessation, smoking cessation or tobacco use cessation has gone up, I guess.

DR. SAMET: Well, we are going to hear, perhaps in November, from the consumer perception research that FDA is doing. That was Portland, Columbus and Charlotte. And I don't know, referring back to Patricia's question, where these cities stand around being smoke-free with their clean air legislation.

Do you know?

DR. ASHLEY: I don't know, right off the top of my head, no.

DR. SAMET: But in terms of what we might learn, we know we're going to hear from FDA eventually on this. I'm not quite sure I know what's in the AAP survey, but perhaps there will be

some other data that's relevant in 18-plus on the perception issue.

Karen?

MS. DELEEUW: I think to sort of maybe clarify what Patricia may be talking about, I know in Colorado we have tobacco-free schools. So the question becomes are dissolvable tobacco products included or not included in those kinds of policies.

DR. SAMET: Bob?

DR. BALSTER: We've mentioned twice now the Virginia Foundation for Healthy Youth, the rather alarming report about the perceptions they had. I look at the report, and they do have the data. But I would suggest asking them for -- we don't know the methods and really much more about what's in there, but that seems like pretty interesting information. So if we could ask them for a full methodology along with that report, I think that could be useful.

They indicate that that was an ongoing study and that there was going to be more data soon. So

if they have that in time for our next meeting, maybe that would be -- we could ask for that, too.

DR. SIMONS-MORTON: Sort of following up on that, that's the only report that we have about adolescent perceptions, unless the American Academy survey or the FDA research includes adolescents.

There may be other ongoing early stage research, though, that we could find out about.

DR. SAMET: And the AAP survey, we heard, was definitely 18-plus, so that would exclude the younger age group. And I assume FDA is looking as hard as you can for any relevant data sources.

FDA indicates yes.

Yes, Fred?

DR. PAMPEL: I don't want to get this too far afield, and there could be too much to learn about. But one thing that comes up, at least in relationship to the harm reduction approach, is that there's a certain proportion of adult smokers who have a very difficult time quitting, and so abstinence is likely not an appropriate approach.

I have no sense of just how big that

population is or how likely it is, and I don't know that you can do a lot of research on it. But maybe there are people here who have some information on that kind of smoker or the size of that group of smokers.

DR. SAMET: Well, there have been various efforts to sort of get at that. I think the question is how specifically that moves us into sort of the broader harm reduction question, and that particular group is -- we haven't sort of set out where we are bounding our discussion. I think that this is something we should probably keep in mind and decide.

For example, there was an NCI report, the target report that probably got at this. That's six or seven years ago, probably, something like that. So there have been some efforts to get at those questions.

DR. PAMPEL: Well, I hope I'm not getting us off track, but it does seem relevant to the uses of dissolvable tobacco as a harm reduction technique, if there are people who can't quit otherwise.

DR. SAMET: I think we'll have to bound how big that track is around harm reduction. I think that was my main point.

Let's see. Abuse liability.

DR. BALSTER: One of the issues here that I think -- I don't know whether there is information or whether there are experts who could be called upon to sort of help us think through this issue, but there is a certain unique feature to these dissolvable products in that the -- especially the nicotine exposure is going to depend an awful lot on exactly the topography of how they're used. I mean, are they left in the gum? Are they put in the mouth? Are they chewed? Are they swallowed?

I mean, there's a tremendous potential for variability of nicotine exposure given even a fixed amount of nicotine in a dosage unit. And I don't know that I -- I mean, I've seen some data from the laboratory people showing us what nicotine levels are from these products, but I don't know that they've explored the variability given the different use patterns. Is it dose linear? So,

1 for example, if people take two of these, do they get twice as much? I'm feeling like we're a little 2 bit lean on that. 3 4 Now, I don't know who -- if there's a way to get data on that or a way to ask someone who could 5 talk a little bit more about the nicotine 6 absorption characteristics, buccally on the tongue, 7 when it's swallowed. That topic area I feel is 8 9 pretty lean. DR. SAMET: So would this be an area, for 10 example, that we could invite Tom Eissenberg to the 11 meeting to perhaps explore more fully what he may 12 have in his data? He would seem to have as much 13 data as anyone, probably perhaps the most on --14 15 DR. BALSTER: I would agree with that. 16

DR. SAMET: Neal, do you have any comments on this idea of, for example, bringing Tom to look more carefully at this data?

17

18

19

20

21

22

DR. BENOWITZ: I think it would be a great idea. I guess my only question is whether we should follow like the standard drug abuse liability testing guidelines and say should these

go through the standard procedures for drug abuse testing or whether Tom's data are sufficient.

I think I made the comment before that Tom's data and Dorothy's data suggested people don't particularly like these products, but that doesn't mean that that's true for everybody.

DR. BALSTER: I'm a little concerned, and I've actually argued with Tom about this in the past. I think there's something a little bit unique about this sort of completely switching modes of use from smoking to a different whole modality of use, and to expect that a one-time test, or maybe even a five-day test, really tells us that much about what someone who actually goes out and buys a whole pack or whatever. And I don't know that the data exist enough on longer-term exposures, where people might find what they like in them as they get more used to them.

Of course, then the question becomes what about people who don't -- really converting from smoking and really are starters on these products. It's a very tricky area in which you're going to

know how to do research.

So I'm not completely satisfied that the abuse liability studies, as they've been presently done, gives us the full range of information to say that, well, people don't like them, because I think that's not going to be quite right if we did it a little differently.

Now, I don't know what to say to do about that. People are doing the studies the way they're doing them. But I think we're a little bit leaner on what we have there.

DR. SAMET: Of course, we could take the opportunity to look at the data that Tom or others have available. And, again, part of what we can do, of course, is make research recommendations, and that's an opportunity to say here are data that are needed to better understand the abuse liability. So if we've looked at all the data and feel it doesn't really -- the studies are too short term, the people in the studies are too atypical or whatever, I think we can then make recommendations.

D, the health risks. I think that is

probably going to be -- our considerations there are probably going to be best based around what we know about the content of these materials, what we know toxicologically. Again, I guess we've heard about some short-term assays and things that are probably not particularly informative, but I don't think we have anything else to turn to.

We have the epidemiological literature on smokeless products generally reasonably well summarized. But any thoughts here about anything we should ask for?

Neal?

DR. BENOWITZ: The first -- and I know that this might be confidential, so this could come to FDA in a confidential way. I really would like to see a complete list of constituents of the products, just so I know exactly what's in them.

Then, also, we heard from Star Scientific data about the potential or lack of generation of increasing tobacco-specific nitrosamines with storage over time, but we haven't heard about that from other products. And that is a concern with

moist snuff, so I'd like to know something about stability and generation of nitrosamines in various storage conditions. I would also like to have more detail about manufacturing processes and reproducibility of products from time to time and batch to batch.

I think it would also be nice -- maybe the FDA can do this or the tobacco companies can supply the data on metal concentrations, because Greg brought that up and we hadn't seen data. So I think I would like to see the data, again to kind of see what the range is and how much variability there is.

DR. SAMET: Let's see. David, do you want to respond a little bit to this around the question of what we can ask for, what might be done in a closed session around, for example, Neal's question about a complete list of ingredients?

DR. ASHLEY: I think there are two sources.

I think one source is, again, to request
information from the tobacco industry to present on
particular issues. There's also information that

FDA has that can be presented in a closed session to TPSAC, because there is commercial confidential information in there. We have received information from the industry in their reporting, and we can present that in a closed meeting.

DR. SAMET: I think to summarize what Neal suggested, it's greater information about manufacturing and sort of, I guess, variability in what is delivered, and then the content question. But that's in reference to dissolvables specifically.

DR. BENOWITZ: And specifically in terms of stability, the issue of generation of nitrosamines with storage, in different storage conditions over time. One of the things about the Swedish Snus is they're supposed to be stored cool, they're supposed to be stored dry. We have no idea what happens to a Camel Orb or whatever if they're in Washington with 100 percent humidity and 100 degrees outside. I mean, we have no idea.

DR. SAMET: So we can go put snus outside today and do an experiment.

[Laughter.]

DR. SAMET: Okay. Anything else on this point?

DR. BALSTER: Yes, if I might. I mean, I'm not sure where we're going to go on this, but it occurs to me that there would be -- that we might find ourselves wanting to consider recommending either labeling products for content of things or even recommending that there might be maximal levels of things.

I don't know that that's at all where we're going to go, but I think in order to be even thinking about going either of those directions, that we'd have to be really, really clear on what exactly it is that we would be asking them to be showing us in terms of the data, if it's in terms of content or in terms of having some kind of a standard.

I'm fairly unclear whether we have a complete understanding of whether just reporting it in PPB of dry weight, or whether it should be done with wet weight, or whether it should be done per

milligram. And, of course, how do those different measures -- and we know from the tobacco literature, from Neal's work, that measuring it in a product isn't always telling us what it is at all in the person. So I don't have a good sense of which of those measures in the products would correlate best with the measures in the people.

So before we would even consider recommending that there would be some kind of labeling or some kind of product standard, I think we've got to be really, really, really clear on what is the unit of measures, and measured exactly how, that we would want to coalesce around.

So at the very minimum, I would like to see some kind of help getting us through the parts per billion versus micrograms per gram versus wet weight, dry weight. I mean, how do we get the equivalency there?

DR. SAMET: I think your comment is a general one that, hopefully, saved, because I think as we gain better understanding collectively about these products and what they deliver to people,

we'll probably have a better understanding.

Mirjana?

DR. DJORDJEVIC: I think we would also need additional information of toxicological testing beyond the Ames assay, neutral red or micronucleus, even if it's necessary to invite somebody who's working on that issue beyond the tobacco industry.

Also, there is a profusion now of new technology, like metabolomics or exposomics, or whatever, which would, in a way, tell what changes are produced using the products like this. And toxicological testing would be very, also, helpful to have both positive and negative control to see how these particular products really compare to no exposure at all.

DR. SAMET: I was struck yesterday when we saw the toxicological data. None of it has been done with sort of more contemporary high throughput techniques. Perhaps that has just not been brought to bear yet, and there's certainly, broadly with chemicals, a lot of discussion about approaches that might be used.

I guess I would turn again back to FDA and 1 say are you aware of people who are carrying out 2 testing who we might want to bring here, or are 3 4 there additional data that might -- studies that might be forthcoming from the companies? 5 DR. ASHLEY: I was going to actually ask 6 that very question to Mirjana about whether she is 7 aware of anybody outside the companies that's doing 8 testing on dissolvable products, toxicological 9 testing. 10 11 DR. DJORDJEVIC: Not particularly on dissolvable products, but are working on smokeless 12 tobacco products. One name that comes to mind is 13 Joseph Guttenplan from New York University, NYU. 14 DR. SAMET: Perhaps you can supply us with 15 16 information of people who might be doing at least some quasi-relevant work. 17 18 Let's see. Accidental ingestion. 19 DR. BALSTER: John, can I just say one final thing on this? I'm not familiar with this WHO 20 21 study group report on product regulation, where I

sort of would have guessed that in there they would

22

have talked about some of this compositional measurement and such. I don't know that report. If it's helpful -- you apparently know something about it. So if you think it's helpful, it would be good to get that report to us.

DR. SAMET: You're not talking about the IARC report. We're just talking about the WHO 2008. David knows it, as well, and they're available on the Web, and we can get you a link to those.

Ingestion we've heard a lot about, and it sounds like FDA is seeking out additional data.

There was a suggestion from John that we learn more about various packaging and how it's covered. We should certainly, I think, get smarter collectively about that.

Anything else we would like to do? We served yesterday as a panel to see if we could open these packages or not, with varying degrees of success, I think. Speaking for myself, they were reasonably senior-friendly.

So anything else we want here? John?

DR. LAUTERBACH: Dr. Samet, in terms of looking at toxicological testing, if we were dealing with a food additive, for example, we'd have the FDA Redbook. Is there anything beyond what's in the FDA Redbook in terms of toxicological testing that we would like to see here?

DR. SAMET: Comments on this? I think we would be interested -- if anybody is doing tests on toxicological assays of any sort on these products, to me, that's what we would be after as opposed to the individual components. And I think that's where Mirjana may be able to point us toward some people who perhaps are doing smokeless studies, and we can find out a little bit more about what they may be doing and if it's anything relevant.

DR. BENOWITZ: I don't know if it's necessary, but it would be easy to do simple studies. From a safety point of view, I've done studies with oral nicotine, giving as much as 6 milligrams. You could easily have someone take three Camel Orbs or four Camel Orbs or five or whatever and just get blood levels. It would be

useful, I think, for different products just to see what the kinetic profiles looks like when some adult swallows them.

Now, I'm not sure how FDA could do that. It would be an easy research study to do technically, if someone would do it, and it might be informative to us just to see what the pharmacokinetics looks like when someone swallows a bunch of them.

DR. SAMET: So this could be a research recommendation perhaps. I don't know. This is not what I heard Battelle proposing to do. I think it would be an interesting exercise in consent.

[Laughter.]

DR. SAMET: But I think your --

DR. BENOWITZ: It's not really a safety issue, because our data don't -- there's nicotine water, they have a bunch of studies that have been done with nicotine tablets orally. We've done them, others have done them. So it's not a safety issue. It's a matter of just getting someone who wants to do it, do the studies.

DR. SAMET: I'm waiting for you to retreat

to your lab and --

[Laughter.]

DR. SAMET: Okay. So ingestion, though, we are anticipating additional data from FDA, if I understand your -- you're going out -- wasn't that in your presentation, Sarah, that you were going to get additional poison control data? Okay.

Features of dissolvable tobacco products that may contribute to tobacco initiation. I think, actually, Patricia has already pointed out -- had some discussion of this. But are there other things about the products, the packaging, people we might want to talk to on this point? And this relates back to the marketing, as well, of course.

DR. BALSTER: Well, as I said, I think that the information we have about the abuse liability of dissolvable products is coming from research in smokers. So if you were going to be looking at this in terms of tobacco initiation, you'd obviously be interested in studying non-tobacco users. That raises a whole series of questions,

but basically that's the data we don't really have.

DR. SAMET: And you could think about how to get it.

I wonder -- actually, jut a question, David and Sarah. If there were very circumscribed kinds of data gathering that might be useful to this committee's efforts -- I'm thinking about some of the kinds of work that was commissioned for menthol. So if we said, well, it would be useful to have focus groups with adolescents looking at these products and their perception -- I'm just making that up, but such data might be useful -- is there a timeline possibility of carrying out work that we see as potentially informative and feasibly done on a short timeframe?

DR. EVANS: The answer is yes, and I can tell you that Consumer Protection Research will address some of those issues. I just did not go into detail today. But we should have that information by the end of September.

DR. SAMET: Could we get more information about what you are doing then? You must have

a -- it sounds like there's a protocol available. 1 DR. ASHLEY: Let us get back to you exactly 2 on what we can do. We definitely -- that is 3 4 progressing well, and I just need to ask a couple of people some questions. 5 All right. Good. But, again, 6 DR. SAMET: we can maybe come back to this before we leave 7 today and say beyond the perception or focus group 8 kinds of work that might be done, other things that 9 could be done. Again, March 23rd, we would need to 10 have any information coming to us probably sort of 11 the January-February timeframe if we're going to 12 consider it. 13 Bruce? 14 DR. SIMONS-MORTON: So this is the one area 15 where the Swedish experience might be very 16 informative, since there is a history of research 17 18 on initiation there. DR. SAMET: And I think we will 19 ask -- somehow we will ask FDA to help us get a 20 21 better handle on the Swedish experience. 22 G, quite similar.

DR. BENOWITZ: Here, I would like to see more of the data analysis like that Greg presented from the NSDUH survey, see if we can get some more of those data and look at it in more detail about current use of smokeless tobacco among youth and dual use and singular use and transitions, just so we know what's going on currently; because I hadn't see those data before, and so they must be available. So if the FDA could get those data and present those to us.

DR. SAMET: Comment on this? It's a question of exploration, further exploration of relevant datasets.

DR. BENOWITZ: Yes.

DR. BALSTER: Part of the issue for this particular thing is going to be, we know there's going to be a group of primary tobacco smokers who are not going to be -- who are dependent tobacco smokers, who are not going to be able to smoke at certain times of the day, like at work, and then they can take one of these products when they need them to suppress tobacco withdrawal. And, of

course, there's some question in the literature on how well they do that, at least in the short haul, based upon some of the studies we read.

But the extent to which people whose tobacco dependence is sort of being disrupted by the restrictions in smoking environments, making them less dependent, is a group of people that, if they are now able to take products during the day to sort of somehow support dependence -- generally speaking, my first impression of the data that is coming from, say, for example, Eissenberg's lab is that on a short-term basis, at least, the dissolvables aren't doing a super great job of suppressing smoking withdrawal symptom scores and things like that.

But I think that's going to be a really critical question as to the extent to which these products can actually, in effect, disrupt -- maintain tobacco dependence, tobacco physical dependence by being able to be used when smoking is not possible.

It seems to me the companies are, in fact,

recognizing that use. And I kind of noticed that one of the Stonewall products, smoke when you need it. Need it, to me, means I need it to not feel badly. I think that whole area is something on which I -- I don't know where we get exactly the data that supports it.

DR. SAMET: I guess we know what's in the published literature. I guess, again, the question will come back, are there unpublished sources that might be valuable, I guess, including some studies.

DR. BALSTER: I can certainly imagine studies that could have been done, for example, in any, quote, "clinical trials" of these products that might have been done in smokers and to whether or not, if there was any type of test to measure dependence in these groups; like, say, for example, using Fagerstrom scales or something like that, and finding out that those folks that intermix the use of tobacco and the dissolvable products were able to retain a higher Fagerstrom score than those people who were in a, quote, "placebo trial." That would be exactly the kind of data that would

1 support my concern. Yes, David? 2 DR. SAMET: DR. ASHLEY: Let me try to answer the 3 4 question you asked a little bit before. protocol we've got for our study, the focus group 5 study, is the protocol that's not been cleared yet. 6 It's not been approved. And so we're a little 7 hesitant to give it to you, because it may actually 8 change by the time it gets through all of 9 clearance. But when that protocol is through, I'm 10 sure we'll be able to provide that. 11 DR. SAMET: Thank you. That would be 12 helpful. 13 So other comments? 14 DR. BENOWITZ: For G, one obvious 15 16 thing -- and we talked about this before. But a key thing is really the dose of nicotine. 17 In fact, 18 Tom's studies show that this doesn't leave withdrawals because these products that he tested, 19 like Ariva, delivered very little nicotine. 20 So this is really a dose response issue, in 21 22 large part, which gets back to the earlier question

about how we're going to define dissolvable 1 products, because this is not a characteristic of 2 dissolvable products, per se; it's how much 3 4 nicotine each particular product delivers. DR. SAMET: Mirjana? 5 DR. DJORDJEVIC: I would just like, also, to 6 return a little bit back to D. Somebody mentioned 7 yesterday about products being targeted to pregnant 8 So maybe utero exposure should be also 9 looked at, especially that these are tobacco 10 11 products which contain heavy metals. And we also know that there is transplacental exposure in utero 12 to cadmium and other heavy metals and they impact 13 on the health. 14 DR. SAMET: Let's go to the next. 15 16 number 2, additional topics, if any. Do we want to hear from the industry? 17 18 Bruce? Well, I do think we want 19 DR. SIMONS-MORTON: to get an update on the test market experience in 20 21 the several states where it's being tried. 22 DR. SAMET: So what would you -- if a

specific request were to be made, what would you be 1 looking for specifically? 2 DR. SIMONS-MORTON: Well, some of it would 3 4 just be who the users are, what their experience was, how they found out about it, their reactions 5 to the marketing. I think it's pretty much what we 6 were told they were going to look at. 7 DR. SAMET: So that would be to RJR and 8 9 Star. Okay. Neal? 10 DR. BENOWITZ: We asked this yesterday, but 11 I will just follow up, with Dr. Curtin to get the 12 basis for the inputs to the model that he 13 14 presented. 15 DR. SAMET: So that could be something that 16 would be provided to us, or are you suggesting that there should be an additional -- a presentation on 17 18 the model itself? 19 DR. BENOWITZ: I'm not sure we need that. Ι would like to see the manuscript, but, more 20 21 importantly, I would like to see the data that are 22 behind the input parameters.

DR. BALSTER: Could I just amend that, as well? I think that's an important issue, too. I was very interested by the potential of that modeling, and I was wondering -- and I gather maybe this is happening -- if FDA's statistician could look at that for us and give us some sort of an assessment of that, those models, or maybe have their own. This would be something that I would like to see FDA's statistician look at, if that's possible.

DR. SAMET: Well, I think this probably depends on the willingness to provide the model at this point, which I gather has been presented.

It's been presented at a meeting, but there's not a paper in the peer-reviewed literature yet.

I guess the question would be, is this model a useful tool. And the answer to that lies both in the questions that Neal asked, which are what are the underlying assumptions, but it lies in the specification of the model itself and the fitting and so on. We've heard it has a probabilistic uncertainty component.

If we think that this model might be 1 something the results of which will be informative 2 to our task, then I suggest we actually have a 3 4 presentation on the model and better understand it. If the code can be provided, and documentation, so 5 that there can be sort of an independent 6 assessment, that would be additionally of value. 7 But I think what I would suggest is that if 8 we want to learn more about it, we ask for a 9 presentation, and that, of course, should cover the 10 issues you've raised. So we would ask for a 11 presentation at the meeting on that. 12 Anything else? The next TPSAC meeting, 13 remember, it's November 2nd or 3rd. I think 14 actually a blizzard is already scheduled for that 15 16 day. [Laughter.] 17 18 DR. SAMET: Yes, Bob? 19 DR. BALSTER: This is pertinent to that last question on there, and that is the issue about 20

product, either through clinical trial type work or

whether or not the markers of a dissolvable

21

22

1 through their other work on following their product, if they see evidence that people who are 2 both smoking and using their products are able to 3 4 maintain their nicotine dependence by sort of mixing and matching smoking plus dissolvable 5 product use, and the extent to which there is 6 evidence that intermixing these allows smokers to 7 maintain their dependence. 8 The question really is are there 9 DR. SAMET: any longitudinal panels that have been carried out 10 that are informative, that are long enough to be 11 informative on that point. 12 They wouldn't need to be 13 DR. BALSTER: overly long, though. I think several weeks could 14 15 give you information about that. I can easily 16 imagine an experiment that could be done in several weeks to give you information. 17 18 DR. SAMET: Okay. Anything else on number 2? 19 [No response.] 20 And number 3, I think we've 21 DR. SAMET: 22 touched on this already, the possibility that there

could be additional analyses. We've talked about survey data that could be looked at. We will hear about, eventually, what the focus groups are doing.

I think, again, it's a very short timeline should any additional studies that could feasibly be done, should we want them done; again, thinking back to both -- whatever the processes you would go through internally to get requests out and so on.

I suspect we're running out of time pretty quickly.

DR. ASHLEY: Yes, I agree. I think we're looking at a couple things here. I think it's great for you guys to be coming up with a list of information you would like to have, and FDA will do every effort to try to get as much of that information as possible. And we realize that some of that would require the generation of new information, which may or may not be available by the time March 2012 rolls around.

So I think it's very worthwhile for you to come up with a list of requests, because in the end, if we can't meet those and if we can't find information, that kind of rolls directly into what

else needs to be done.

So I think this is very worthwhile for you to propose those ideas, and we will take those under consideration and see what we can and cannot deliver.

DR. SAMET: So let me read down what I have as sort of quasi-task list. So, one, that we are going to need to develop a working definition of what a dissolvable is and how this fits within this broader category of smokeless products.

Second, we said that we think that the snus experience generally and the Swedish experience in particular could be informative for our dissolvable task. Maybe one of the circumstances that has sort of lessons learned that can be applicable to the dissolvable story, I think -- and this goes back -- that we would probably ask the FDA to identify the relevant literature on the Swedish experience and have a presentation at our next meeting on that, and I think, hopefully, distribute to us a set of critical papers so that we can all read them.

Related to that, and let's make sure I've heard this right, we talked about the marketing of snus in the U.S. as an example of the smokeless product brought into the marketplace in sort of the current environment around smoking indoors and its restriction, and looking at how the marketing had been done could be useful for dissolvables. That's what we said.

Do we want to ask either FDA to bring us information about marketing of snus or hear presentations from the companies, and have I phrased our desires correctly?

[No response.]

DR. SAMET: Okay. We said that the marketing -- again, because there's actually been such limited marketing so far of dissolvables, that the marketing of snus, the approaches might be useful to understand how a product is brought into an environment where the opportunities to smoke indoors, workplaces, public places, are restricted.

These products have been marketed over the last several years, so that there is some

experience to look at and try and understand and understand what that experience might inform us with regard to dissolvables.

As inarticulate as what I said may have been, that is what we said.

DR. BALSTER: I agree with that. And my preference, I guess, would be to send the same set of questions that were sent about the dissolvables to those American manufacturers of those snus products and have them present.

I don't want to micromanage the next meeting and don't know whether that would be a high priority or not, but I think that would be certainly a way to get a comparable set of information on those products as what we got on the dissolvables.

DR. SAMET: Okay. So I think, David and Sarah, at least the question of approaching the companies on the snus marketing for presentations is one possibility for the next meeting.

We wanted to get more information about the study carried out in Virginia. That possibly could

be a group that we invite. At the least, we could learn more about the approach and methods.

Presumably, that could be a query to them, and we can make a decision about whether there's any value in having them come and present whatever data updating there may be and have some interaction with them.

So I think, at the least, everybody who hasn't seen it, if you wander through the public docket comments, it's in there somewhere. There are several PDFs related to it, and you can look at it.

We did say we would like Tom Eissenberg to come to our next meeting and that we can, I think, provide him with some specific guidance on what we want to ask him about. That had largely to do with better understanding of variability among people and whatever other insights he's gained from published studies and newer work.

On the question of -- there was a broad set of issues around content, ingredients, manufacturing, and the generation of tobacco-

specific nitrosamines, some issues that Neal 1 raised. And I think this would be in the form of a 2 query to the companies. 3 4 Then there was a question, just the general issue was anybody carrying out toxicity testing 5 that we were not aware of for these products. 6 Then, finally, any additional survey data 7 analysis, following up on some of whether Greg 8 showed us and whatever else might be available. 9 And, in part, this would I think involve 10 interactions between FDA and CDC. 11 Again, I think I heard two specific things 12 related to possible industry presentations at the 13 next meeting, the additional -- any updates to the 14 test marketing experience from the companies with 15 16 dissolvable products, and then a presentation of this population model. 17 18 So those are my -- the list. Are there any 19 additions that anyone wants to make, or subtractions? 20 MS. KELLER: (Inaudible - off mic). 21 22 DR. SAMET: I'm sorry. The public comment

period is over. If you have something that would 1 contribute to our discussions and you want to grab 2 the microphone, that's fine, but --3 4 MS. KELLER: Okay. I'm sorry. On the question about trying to get a handle 5 on how many smokers are what you refer to as 6 hardcore, who would have a great deal of difficulty 7 quitting, I believe John Hughes at the University 8 of Vermont has done some work in this area. 9 DR. SAMET: Thank you. 10 11 Again, for those of you who are interested, there was this monograph -- help me out, the 12 hardening the target -- what was the name of it? 13 DR. DJORDJEVIC: Maybe 14 after the 13. 14 [Laughter.] 15 16 DR. SAMET: Don't mention monograph 13 --DR. DJORDJEVIC: The 13 was in low yield 17 18 cigarettes, so hardening was following up that 19 monograph. DR. SAMET: So there is an NCI monograph on 20 this, again, with some fairly extensive data 21 22 analyses, probably, though, relating to data that's

probably, at the newest, 10 years old now, I would think.

I think, again, Fred, as we move forward, the question of how we bound what we're doing, I think we may need to come back to the issue you've raised.

So we have this specific list.

Caryn, do you have all this in your notes?

And I've got it in mine. So if we need

clarification, we can do that.

The other thing I will do is I'm going to return to the note I wrote somewhere last summer, sort of framing out some of the thinking about menthol. I do want all our new members to look carefully at the menthol report, and I'll see if both that note I wrote earlier and perhaps some additions to it would be helpful.

I think if anyone has thoughts about this issue of the working definition, again, I think we should try and get some of this thinking laid out before we have our next meeting. So if Neal, for example, or anyone else who is ruminating about

this, I think we can just begin to develop some 1 thoughts about a working definition. 2 I think we've done our work. Let me see. 3 4 We're somewhat launched here, and I think it's going to be a challenging topic. 5 Mark, if you're still with us, do you have 6 anything you want to add? 7 DR. CLANTON: I am still with you and 8 nothing to add. 9 DR. SAMET: Okay. Thanks. 10 DR. SIMONS-MORTON: The issue of definition 11 and of regulation seems like a difficult one. 12 important to define, but, also, it might be helpful 13 for someone at FDA perhaps to sort of go through 14 15 the current regulation of smokeless tobacco and 16 implications of applying those regulations to dissolvables and the alternative approaches. 17 18 DR. SAMET: David? DR. ASHLEY: Can you give me a little more? 19 I mean, there are some very specific parts of the 20 statute that refer to smokeless as far as labeling. 21 22 I'm trying to think if there's anything else that

1 deals with smokeless that doesn't deal with tobacco products as a whole. I may be missing something. 2 MS. DELEEUW: I think some of the 3 4 regulations in the master settlement agreement are around marketing, although, again, nothing is 5 supposed to be marketed to anyone under 18 years. 6 7 But there may be some information there that might prove useful. 8 DR. SAMET: Okay. Anything else? 9 [No response.] 10 Adjournment 11 DR. SAMET: Okay. I think we are done, and 12 I want to thank everybody. Thanks to the public, 13 our commenters, and to the industry for 14 15 presentations yesterday. And I guess the dissolvable story has started. See everyone in 16 November. 17 18 (Whereupon, at 11:30 a.m., the meeting was 19 adjourned.) 20 21 22